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Review Article

How confident can we be in the current guidelines for exiting cervical screening?

Patti E. Gravitt[a,*], Rebecca Landy[b], Mark Schiffman[c]

[a] Milken Institute School of Public Health, The George Washington University, Washington, DC, USA
[b] Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary, University of London, Charterhouse Square, London EC1M 6BQ, UK
[c] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, DHHS, Bethesda, MD, USA

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ABSTRACT

Current US guidelines recommend against cervical screening beyond age 65 in women who have had adequate negative screening. In anticipation of the next round of evidence review and guideline updates, we provide a critical review of the evidence supporting the exiting recommendation in the US, highlighting both practice changes and new insights into the epidemiology and natural history of HPV and cervical cancer. Current recommendations are based, by necessity, on cytology alone, and will be limited in generalizability to evolving screening strategies with co-testing and primary HPV testing. The lack of empirical data to define what constitutes 'adequate recent screening with negative results' is compounded by difficulties in predicting future risk without consideration of concepts of HPV latency and cohort effects of changing sexual behaviour in US women over time. We urge caution in extrapolating past risk experience in post-menopausal women to today's population, and suggest study designs to strengthen the evidence base in well-screened older women. We further recommend building the qualitative evidence base to better define the harms and benefits of screening among older women. Extending the lifetime of screening is a matter of finding the appropriate balance of benefits of cancer reduction and limitation of harms and costs of 'overscreening'. This will require moving beyond current emphasis on number of colposcopies as the metric of harm. Our commentary is meant to stimulate intellectual debate regarding the certainty of our existing knowledge base and set clear research priorities for the future.

Cervical screening reduces the incidence of and mortality from cervical cancer by identifying precancerous lesions that can be treated, thereby preventing incidence, or by identifying cancer at an earlier stage, reducing mortality. Screening guidelines differ between countries with established screening programmes; these differences include screening modality (cervical cytology and/or molecular testing for the causal agent, human papillomavirus or HPV), screening interval, and the ages at which screening begins and ends. A robust evidence base has emerged from a combination of randomized controlled trials and observational studies in population-based registries to inform recommendations for screening modality and screening interval. In contrast, data to directly inform the appropriate age and conditions under which women can safely end routine cervical cancer screening is largely absent, resulting in recommendations that rely on interpretation of surveillance trends, expert opinion and mathematical modelling. As part of ongoing updates to US cervical cancer screening guidelines, we discuss the potential limitations of the available evidence that weighs heavily in current exiting guidelines, with respect to evolving screening strategies and increased understanding of the nuances of the natural history of HPV within an individual over time. Additionally, we identify critical data elements needed for future guideline evaluations.

1. Current recommendations – age to exit screening: divergent opinion on quality of evidence

The 2012 USPSTF (United States Preventive Services Task Force) and ACS-ASCCP-ASCP (American Cancer Society- American Society for Colposcopy and Cervical Pathology- American Society for Clinical Pathology) guidelines recommend against screening for cervical cancer in women older than age 65 years who have had adequate prior screening, no history of CIN2+ (Cervical Intraepithelial Neoplasia grade 2 or higher) within the last 20 years and are not otherwise at high risk for cervical cancer (U.S. Preventive Services Task Force, 2012; Saslow et al., 2012). Adequate prior screening is defined as 3

* Corresponding author.
E-mail address: pgravitt@gwu.edu (P.E. Gravitt).

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consecutive negative cytology results or 2 consecutive negative co-tests within the 10 years before ceasing screening, with the most recent test occurring within the past 5 years. This recommendation was graded 'D' by the USPSTF, meaning that 'There is moderate or high certainty that the service [extended screening past 65] has no net benefit or that the harms outweigh the benefits', yet the same recommendation was classified as 'weak' by the ACS-ASCCP-ASCP, due to the choice of exiting age being dependent on 'the judgment of the expert panel members about a favourable balance between the benefits and harms of screening older women'. These recommendations are based on modelling studies and expert opinion, as there was very little empirical data available on which to base these recommendations. The current draft USPSTF guidelines continue to recommend these exiting criteria, and we are not aware of anyone challenging this upper age limit (U.S. Preventive Services Task Force, 2017).

However, evidence published since the 2012 guideline review shows that the cervical cancer incidence in women with 3 consecutive negative cytology tests (within 15 years of exiting) is around 4/100,000 (Dinkelspiel et al., 2012; Castanon et al., 2014) per year, or a cumulative incidence of 60/100,000 by age 80 years. Without a pre-defined threshold for acceptable risk, it is unclear whether the current recommendations of 'no net benefit relative to harms' are supported in light of these data. In addition, as the adoption of co-testing or primary HPV testing in women over age 30 becomes more universal in the US, the risks from cytology testing alone become less relevant. There are as yet no empirical data to estimate similar absolute risks following 2 consecutive negative co-tests by age 65 years, as sufficient follow up time has not yet passed. Even with cytology testing, a wide range of screening intervals are used, and it is not known whether the protection from 3 negative screens taken a year apart (which would fulfil the exiting criteria) is the same as the protection with a screening interval of 3 years.

There does not appear to be consensus among guideline authors regarding the incidence threshold below which screening is no longer recommended. For example, a recent review of evidence in Australia (Medical Services Advisory Committee A, 2013) noted that 'cervical cancer incidence and mortality remained high in older age groups', referring to incidence rates of 10.2–11.8 per 100,000 women aged 65–79, increasing to 14.2 in women aged 85+ (Australian Institute of Health and Welfare, 2016). Yet, evidence reviews in the US considered SEER reported incidence rates of 10.6 in women 65–74 and 8.2 in women ≥75 years, to be low (National Cancer Institute SEER Program, 2016). In addition to apparent differences in threshold determination, US rates increase nearly 2-fold with appropriate adjustment for hysterectomy (Rositch et al., 2014; Beavis et al., 2017), with evidence of ICC rates increasing up to age 85 in hysterectomy-adjusted data (White et al., 2017).

2. What evidence do we need?

The benefit of screening is ultimately measured by the reduction in incidence of advanced cervical cancer. To adequately estimate this in the context of screening cessation, we would ideally want estimates of the absolute risk of invasive cervical cancer (ICC) from age 65 following the exit screen in women, stratified by screening history. This would allow comparison of multiple exiting criteria. Since there are strong cohort effects influencing the risk of cervical cancer, older data indicating that it is safe to exit screening at age 65 (Mandelblatt et al., 1986; Sung et al., 2000) may no longer be reassuring for women currently approaching age 65. Similarly, retrospective analyses of old data will not be able to provide the answers. Additionally, since widespread co-testing or primary HPV testing adoption is a recent development, the accumulation of this data will take at least another 15–20 years.

Therefore, the next several rounds of guideline reviews will continue to be limited. Despite this, we review below several opportunities for prospective data collection which may provide interim guidance regarding the safety of exiting under currently recommended rules. In addition, we highlight several relevant epidemiological biases that may have important impacts on the interpretation of surveillance data that guide expert opinion.

3. New study designs to guide exiting guidelines

Although ultimately the goal is to demonstrate the protection of an exiting strategy against advanced cervical cancer, it is possible to gain insight into the safety of our exiting strategies by using CIN3/AIS (adenocarcinoma in situ) as a surrogate marker of cancer risk. For example, using a cross-sectional study design, women could be consented to a post-exit cotest with a concerted attempt at endocervical sampling 5–10 years after their exiting screening test, and CIN3/AIS/cancer (CIN3+) detection rates could be compared by pre-exit screening history and the time since last negative screen. Whilst this design gives some relative comparison of potential cancer risk by screening history, it does have important limitations. In addition to requiring a large sample size of elderly women to agree to participate, the well-described diagnostic challenges in detecting pre-invasive disease in post-menopausal women whose transformation zone cannot be fully seen and who have epithelial atrophy may increase the risk of outcome misclassification. A similar design could be employed using tissue from hysterectomy for benign conditions linked to screening registry data if these are available.

4. New evidence since last review

The evidence provided to support the current recommendations included reduced benefit due to (i) precancerous lesions (with a threshold of CIN2) and cancer being rare after age 65 years, (ii) low prevalence of the dozen high risk (HR, cancer-associated) types of HPV (~5%), and (iii) unlikely progression of new infection in older women to cancer in the remaining lifespan. These perceived reductions in benefits were countered with an increased harm associated with screening, since diagnosis of neoplasia is more difficult in post-menopausal women (Elit, 2014). Since these recommendations were made, evidence has emerged which calls into question the validity of the interpretation of both the surveillance data and the natural history of HPV infection.

5. Does the evidence show that invasive cervical cancer and CIN3 are rare in older women?

In the US, high-risk (HR)-HPV prevalence has a characteristic age-specific pattern, peaking around the age of sexual debut with a subsequent decline, reaching a plateau by age 40 of approximately 5–10% prevalence (Gage et al., 2015), or even increasing beyond age 40 (Bosch et al., 2008). However this could change in the near future due to the delayed impact of changing sexual behaviors over time (Liu et al., 2015; Ryser et al., 2017). When explaining the guidelines, research into 'risk factors that move lower-risk women (such as older women with normal cytology findings or negative HPV test results) into higher risk categories (such as older women with positive HPV/negative cytology results or exposure to new partners)' (U.S. Preventive Services Task Force, 2012) was identified as being important. One such risk factor may be the lifetime number of sexual partners. Older women in these surveillance estimates represent birth cohorts with half the average number of lifetime sex partners (LTSP) compared to younger women/birth cohorts (Liu et al., 2015). Correcting for this cohort effect by stratifying age-specific HPV prevalence by number of LTSP reveals a much higher plateau of HR-HPV prevalence in women with 5 or more LTSP (Gravitt et al., 2012), which appears to be largely attributable to cumulative sexual history rather than new sexual partnerships at older ages (Rositch et al., 2012).

Thus, the low prevalence at older ages observed in cross-sectional