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Editorial

State of the Science: Cervical cancer screening in transition ☆,☆☆

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Introduction

The age of cervical cytology as the dominant modality for screening for cervical cancer and its precursors began with enviable simplicity. Women received a Pap smear at whatever age they first appeared in the gynecologist's office, and preferably annually thereafter. Paps were either positive or negative, colposcopy for those with positive Paps involved 0 or 1 biopsy in most cases, and the phrase "return to routine screening" meant "have another Pap in a year". In the last 15 years, every single aspect of that simpler age has fallen by the wayside, and clinical practice has become dramatically more complex and less uniform. The evolution of clinical recommendations has been made more contentious by the inability to perform randomized clinical trials to resolve the most important issues. A milestone in the transition to the age of molecular screening was formally marked on March 12, 2014, with the unanimous recommendation of an FDA Advisory Panel to approve a specific HPV test for use as the primary screening tool in place of cytology. Until that transition is complete, complexity, frequently changing recommendations, and acrimony reflecting imperfect data and conflicting priorities are to be expected.

The first crack in the wall was the tacit recognition, implicit in the development of the Atypical Squamous Cells of Undetermined Significance (ASC-US) category, that some cervical cytology results are neither positive nor negative. The prevalence of this diagnosis and the recognition that this category contained within it more women with CIN2+ than any other cytologic result including HSIL [14], offered the first opportunity for clinical application of the insight for which Harald zur Hausen was awarded the Nobel Prize in 2008 [27] that the presence of high risk HPV was a necessary but not sufficient condition for the development of virtually all cervical cancer [36]. Subsequent study of the natural history and ubiquity of high risk HPV carriage demonstrated that most infections and their coincident cytologic and histologic abnormalities resolve promptly and are best unrecognized [24,26]. This understanding led to efforts to provide the most accurate test at the longest possible interval, prompting the approval and recommendation of Pap plus HPV cotesting at 3 year intervals, as an effort to provide cancer protection similar to annual Paps [8] with fewer tests and visits, and less recognition and treatment of transient abnormalities that would have resolved on their own.

The principle of equal management for equal risk, and the choice of measures of risk

The disadvantage of introducing screening systems involving multiple tests is that the results may be discordant, and that the increased number of combinations of results dramatically increases the difficulty in crafting (and remembering) the appropriate management for each. In 2007, Castle et al. introduced the concept of equal management for equal risk, recognizing that there were now multiple screening outcomes that were associated with similar risks of the presence of cervical cancer precursors or cancer, and hence should be managed in a consistent way based on that risk [4]. This principle was extended and applied by Katki et al. in 2013 [12], who recognized that while the immediate risk of CIN3+ should dictate who is referred to colposcopy, that same risk over time could be applied to estimate the most appropriate followup interval. This fundamental insight informs the most recent recommendations for management and followup of abnormal screening test results and the discussion of different primary screening tests and intervals that follows, with the sole caveat that cancer is the most relevant endpoint for evaluation of screening strategies, and should be used in preference to CIN3+ when it is available, in contrast to evaluations of test performance, for which CIN3+ is the correct endpoint. It can be appreciated that CIN3+ is not the right measure of risk for comparison of screening systems when the screening is changed to more

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☆☆ **Condensation**. The transition between cytologic and molecular screening is in progress, with a proliferation of screening choices involving different levels of harms and different risks of cancer.

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sensitive testing and thus detects more CIN3. Because CIN3 is so much more common than cancer, it apears that the outcome is worse, i.e. the risk is higher with the new screening strategy, when in fact the protection from cancer is staying the same or improving. This is exactly what we saw in Kaiser Permanente Northern California (KPNC) when we introduced cotesting: CIN3 detection underwent a sustained doubling and AIS detection a sustained 6-fold increase, while cancer has diminished slightly. This would be perceived as a worse outcome if CIN3+ was the endpoint used to evaluate this change.

Evidence-based medicine and cervical screening

The discussion of the benefits and harms of cervical cancer screening programs is exceedingly difficult for (and with) those for whom "evidence" begins and ends with randomized controlled trials (RCTs). It is possible to do RCTs for the purpose of comparing the efficacy of screening tests in one or two rounds of screening, and a number of these have been done, usually comparing cytology to HPV testing or cytology to cytology plus HPV testing at a fixed interval [2,15,25,30]. These can be accomplished because CIN3 is relatively common and can occur within a short time of HPV exposure [16]. What has never been accomplished and should not be anticipated is a RCT comparing the results of different screening strategies on the occurrence of cancer, which is (from the perspective of the patient) the relevant outcome measure. Cancer is also sufficiently rare in screened women (single digits/100,000/year) that hundreds of thousands of women would need to be involved in a RCT over decades to see statistically significant differences in cancer risk between arms. Other important associations, including the association of Loop Electrosurgical Excision Procedures (LEEPs) and prematurity among others, cannot be investigated with RCTs for obvious ethical reasons.

The second issue that confounds discussions of cervical screening with those used to making judgments based on RCTs with prompt and common endpoints is the time course of the development of cervical cancer. Screening failures do not manifest themselves as cancer immediately, recognizing that approximately 30% of untreated CIN3 becomes cancer in 30 years [19], and the consequences of screening (both positive and negative) accrue over a woman's lifetime. This is an essential insight because it means that the application of the customary annual measures of disease and death to cervical screening has the effect of trivializing the differences between different screening modalities and intervals. RCTs to compare the same test at different intervals are equally problematic — a trial comparing 3 rounds of screening at 4, 5, 6 or 7 year intervals that was recently discussed would require 21 years of followup after accrual was completed. The pace of viral carcinogenesis simply requires a different perspective.

We are left, as a consequence, with observational studies and modeling, neither of which is considered "evidence" among those trained to evaluate interventions for which RCTs can evaluate prompt and common outcomes. Nonetheless, those charged with making decisions concerning the care of patients are obligated to try to parse the likely consequences of different screening strategies based on the information that is available. Given the uncertainties involved, some disagreement is to be expected, particularly in the evaluation of competing risks, and the advent of new information will require uncomfortably frequent reappraisal of previous opinions. *Note that the current screening recommendations are based on CIN3+ risks at 3 and 5 years after a negative screen, rather than cancer risks over a lifetime, as discussed below* [31].

Whom to screen

Since 2010, initiation of screening at the age of 21 had been recommended because the cancer risk below this age is vanishingly low and minimal abnormalities are ubiquitous [23]. This recommendation is unanimous among the American College of Obstetrics and Gynecology (ACOG), the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), the American Society for Clinical Pathology (ASCP), and the United States Preventive Services Task Force (USPSTF).

ACOG, ASCCP, ASCP and the ACS agree that women should discontinue screening at age 65 if they have had three negative Paps or two negative cotests in the preceding 10 years. Those who have been previously treated for CIN2+ should continue screening for at least 20 years following treatment, because the risk of cancer for such women has been reported to remain as high as 56/100,000/year despite treatment [34]. Note that this information comes from the age of screening with cytology only.

Test and interval recommendations

As of 2012, ACOG, ACS, ASCCP, ASCP, and USPSTF recommend screening with cytology every 3 years for women age 21 to 29 years. For women 30 to 65 years, ACOG, ACS, ASCCP, and ASCP recommend screening with cotesting every 5 years in preference to cytology every 3 years [31]. The USPSTF recommends either of these screening modalities and intervals without preference. These recommendations represent a continuation of the previous USPSTF recommendation for 3 year cytology. Five years after a negative cotest the risk of CIN3+ is similar to the risk of CIN3+ 3 years after a negative cytology [31]. Modeling indicates that the cancer risks are the same or lower 5 years after a negative cotest than 3 years after a negative cytology [17], and unpublished data from KPNC suggests that 5 year cotesting will eventually prove to be associated with less cancer risk than 3 year cytology. These recommendations represent a change for ACOG, which had historically recommended an annual interval if cytology is used alone, at least at the initiation of screening, and more recently condoned 3 year cotesting, which in clinical practice produces cancer rates similar to a recommendation for annual cytology [8].

This apparent decrement in the level of cancer protection may decrease clinician and patient confidence in and compliance with the current recommendations. Cancer risk is measurably different between annual and 3 year cytology. The relative risks of cancer reported between one and three year cytology range from 1.3 to 4.7 [33,9,20,11]. Miller et al. documented a doubling of cancer risk between 1 and 3 years in the KPNC population and Sawaya et al. showed that this increase in risk is not ameliorated by 3 previous negative Pap smears [21,32]. We have now reviewed the screening results of 500 women subsequently diagnosed with cancer who were previously screened at least once in KPNC between 2003 and 2012. The Weibull estimate [12] of cumulative cancer risk in women ages 30 to 64 at 12 months following a single negative Pap is 0.0101% (0.0082%–0.0125%), and at 36 months the comparable risk is 0.0214% (0.0183%–0.0250%). These risks may seem quite small, but they pertain only to a single negative test, and as noted above, the clinically relevant interval for evaluating the consequences of screening decisions is a woman's lifetime. Modeling permits us to examine the lifetime consequences of screening choices, placing the magnitude of the risks into clearer perspective. Kulasingam et al. have published modeling of this nature done for the most recent USPSTF guideline revision, showing that if 5 year cotesting is implemented in place of 3 year cotesting, an additional one in 369 women who were compliant with screening recommendations would be diagnosed with cancer, and an additional one in 1639 women who were compliant with screening would die of cervical cancer [17]. In KPNC we have 1,008,855 women who screened once or more in the 42 months prior to 12/31/12. Over the lifetime of a group of screening participants of this magnitude, the model predicts that 2734 additional cervical cancers will be prevented (total 4772 instead of 7506), and 615 additional deaths from cervical cancer will be avoided (total 747 instead of 1362) if we retain our current 3 year cotesting intervals instead of moving to 5 year cotesting. Every cancer prevented by staying at 3 year cotesting would require 92 additional colposcopies, and every death prevented would require 408 additional colposcopies. These