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Equal Management of Equal Risks: What Should be Used as the Standard for Cervical Cancer Prevention?

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MODERATOR STATEMENT

Rebecca B. Perkins, MD, MS

We are entering a new era of cervical cancer prevention. With the introduction of highly effective human papillomavirus (HPV) vaccines and advances in screening technology, the elimination of cervical cancer may be an achievable goal. The *International Papillomavirus Society* call to action states: "Combining HPV vaccination at high coverage for adolescents and high coverage of cervical screening, with appropriate treatment of all women, can eliminate cervical cancer as a public health problem. Recent modeling suggests that, with the tools available, elimination of cervical cancer in local populations is achievable within our lifetime."[1]

New technologies including HPV vaccination, HPV testing, and other technological advances have the potential to revolutionize prevention—but only if we know how they can be used most effectively and if we can also convince providers and patients to use them as recommended. Historically, cervical cancer prevention relied on a single screening technology, the Pap test, and a single diagnostic technology, colposcopy. Pap testing has limited predictive value and offers only short-term reassurance against cancer development, so frequent repeat testing over a woman's lifetime is needed to prevent cancer. HPV testing detects far more lesions with the first round of screening, and repeated negative testing provides substantial, long-term reassurance that cancer will not develop.[2] In the setting of HPV vaccination, which essentially eliminates infection with the most virulent oncogenic viral types, positive screening results become less ominous, as they are more likely to reflect transient abnormalities than precancerous lesions.[3]

Therefore, our current system of screening and management must change. We need to avoid overscreening and overreferral of women at low risk for cervical cancer: those who have received HPV vaccination or have multiple negative HPV tests. However, at the same time, we must ensure adequate screening, diagnosis, and treatment among those at the highest risk, including women with persistent HPV infections, recent treatment for precancerous lesions, and those who have been neither vaccinated nor recently screened.

Historical standards for screening and colposcopy referral were based on Pap testing because that was the only test available. Women with an abnormal Pap test result were referred for colposcopy, and women with negative results were typically rescreened annually. These recommendations reflected the limitations of Pap test technology and were the best we could do at the time. This is no longer the case, however, because of advances in screening technologies and improvements in our understanding of the natural history of HPV infection and carcinogenesis. The risks of precancer after a Pap test, HPV test, or co-test vary substantially and are affected by a woman's vaccination and screening history. Negative results on different tests or even the same test result in different patients can yield substantially different risks of precancer. Therefore, the guidance for performing clinical actions, such as repeat screening or colposcopy, must evolve.

Because we can predict the risk of precancer with a given combination of screening results and patient history, we must decide as a society what risks are sufficient to prompt additional actions, such as immediate treatment, colposcopy, or repeat screening. How do we pick these thresholds? In this forum, we address the question of what standards of cervical cancer protection should be followed as we move forward to create new, more precise screening and management guidelines.

SIDE 1

The Standard for Cervical Cancer Protection Provided to Cervical Cancer Screening Participants Should Remain That Previously Afforded by Annual Pap Smears

Discussant: Walter K. Kinney, MD

Why Should We Undertake This Discussion?

Screening tests, screening intervals, and methods of evaluating women with abnormal results are entering an era of unprecedented choice and technological advancement just as the cancer risk in the population entering screening is falling as a consequence of vaccination. The effects on test performance and changes that will unavoidably occur in the next few years would be less disruptive, and recommendations from different organizations less disparate, if we could achieve agreement about what screening was intended to accomplish and what was required for successful implementation of changes in actual clinical practice. It is this discussant's belief that the preferences of the clinician and patient communities will need to be heeded if widespread practice changes are to occur and that failure to take those preferences into account will result in recommendations of great methodological purity that are not followed by anyone who can avoid them.

History

1. Until very recently, the commonest practice in the United States was to recommend annual Pap smears. Although it is freely acknowledged that this was without a clear scientific rationale, significantly insensitive and profoundly inefficient, it was also responsible for a dramatic drop in the incidence of invasive cervical cancer and became the US standard of care.
2. There is no credible evidence anywhere that Pap smears at 3-year intervals produce the same cancer protection as annual Pap smears. The fact that randomized controlled clinical trials with cancer endpoints cannot be conducted in no way changes this assertion. Gage et al.[4] have published the observed risk of

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cancer at 1 year and at 3 years after a single negative Pap, and the risks are 3-fold higher at 3 years, and the confidence intervals are widely separated.[4] Sawaya et al.[5] have published that this increase in risk is present even in women with multiple negative preceding Paps. Although the absolute risks in the few years immediately after a single test are small, the cumulative risks over a woman's lifetime are much more intimidating. Although the assessment of absolute risks differs among models, there is no model that suggests that the cancer protection from annual versus 3-year Paps is identical.

3. It has been the preference of the US Preventive Services Task Force (USPSTF) to recommend Pap smears every 3 years. This longstanding recommendation has had no discernable effect on clinical practice in the United States outside of federally funded clinics.
4. In Kaiser Permanente Northern California, it was possible to change the median screening interval to 36 months within 2 years of the introduction of co-testing in 2003. This was remarkable because a recommendation for 2-year-interval Pap screening made in the same organization in 1996 was widely ignored by patients and providers. Immediately before the adoption of co-testing in 2003, two thirds of female member were still being screened annually. The ability of the providers to tell their patients (and the Medical Assistants, without whom no practice change can succeed) that 3-year co-testing provided cancer protection at least as good as annual Paps was a significant difference from the 2-year Pap recommendation and in the opinion of this discussant essential to the successful adoption of co-testing.

Current Setting

1. The population risk of invasive cancer is falling because of the widespread introduction of HPV testing into screening and the initial effects of vaccination. At the same time, there is a tidal wave of innovation nearing our shore, both in the understanding of what serial combinations of screening results actually indicate with regard to risk,[2] and in new tools for screening, including extended genotyping, the first of the biomarkers[6] and computerized cytology interpretation. Management of a given patient based on her actual risk[7] will very soon become sufficiently complex that computerized assistance will be essential for the harried practitioner, presumably in the form of a cell phone app.
2. Evolution of screening practice will be essential for a rational response to the impending sea changes described previously.
3. The unwillingness of patients and providers to consider changes that they feel may compromise cancer protection is manifested in the widespread rejection of 5-year screening intervals in clinical practice and in the hostile response to the USPSTF's new draft recommendations from a range of experts, including the Society of Gynecologic Oncology representative.

Assertions

1. Successful changes in US clinical practice are going to require the demonstration that expert bodies actually share the view of clinicians and patients that cancer prevention is paramount. Currently, it is clear to the casual observer that this is not the case. Clinicians are entirely excluded from the guideline process to make sure that the result is not contaminated in any way by their input. The resultant recommendations demonstrate great methodologic purity at the expense of having any effect on clinical practice.
2. Patients' principle reason for undergoing cervical cancer screening is to prevent cervical cancer, not to prevent colposcopy. Neither patients nor providers consider colposcopy to be a "harm."
3. When considering the harms of screening, the clarity of pathologic diagnoses and the necessity of treatment of cervical intraepithelial neoplasia (CIN) 2 in women who have not completed childbearing must be considered.[8,9] Although treatment of CIN 3 is the cornerstone of cervical cancer prevention, immediate excisional treatment of CIN 2 is unnecessary for cancer prevention for many women aged 21 to 39 years.[9] Therefore, the LAST pathology recommendations, which report histology in a way that does not distinguish women who need to be treated for CIN 3 from the larger group with CIN 2 that may not need immediate treatment, are a disservice that will result in a lot of unnecessary excisional treatment.
4. Screening interval extension is not an equitable harm-reduction modality for women who harbored vaccine-type HPV at the time of vaccination.
5. Maintenance of cancer protection at the level provided by annual Paps will not be onerous. Reductions in screening intensity are not the only path to reduction of colposcopy and excisional treatment. Multiple negative HPV tests confer protection significantly beyond that of a single test.[2] New technology will permit more specific triage of women with positive HPV tests, limiting colposcopy rates.[6] Women who are HPV positive with less risky HPV types may not require immediate colposcopy. Understanding of the natural history of HPV oncogenesis suggests that a first abnormal screen after a negative HPV test will not carry the same risk as the same abnormal without knowledge of the HPV history, and in some instances, the new abnormal will not require colposcopy. Improved understanding of the risks of equivocal histologic diagnoses will permit reductions in follow-up intensity.[9]

Recommendations

1. Reaffirm that the goal of changes in screening practice is to decrease harms and resource utilization without compromising cancer protection. Recognize that the standard of cancer protection in US screening practice is and has been that of annual Paps.
2. Optimize specificity of screening using new technology and new understanding of individual patient risk.
3. Patients unanimously and instinctively understand any reduction in screening as representing increased risk for them in the service of profit. Make sure that providers are prepared to explain why this is not the case or be prepared to have any new recommendations ignored.
4. Significant changes are inevitable and will occur soon. They do not have to be adverse. Please lead, follow, or get out of the way!

SIDE 2

The Standard for Cervical Cancer Protection Should Carefully Weigh the Risks and Benefits of Screening and Treatment

Discussant: George F. Sawaya, MD

The current debate addresses a potential important difference in cancer reduction conferred by annual cytology screening compared with triennial cytology screening. Here is some backstory.

In 2003, the USPSTF found no direct evidence demonstrating that annual cytology screening achieved better outcomes than screening every 3 years. Thus, it recommended cervical cancer screening "at least every 3 years."[10] Modeling studies cited at that time estimated that annual screening reduced cancer risk by 94% compared with 91% conferred by triennial screening. In 2012, the USPSTF more resolutely recommended screening every 3 years based in part on a more thorough enumeration of the harms incurred by too-frequent screening, including excess invasive

procedures as well as surveillance and treatment of lesions destined to resolve without clinical consequence.[11] The USPSTF, however, did not explicitly discourage annual screening.

Guidelines published that same year by the American College of Obstetricians and Gynecologists[12] and those by the American Cancer Society, the American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology,[13] on the other hand, actively discouraged annual cytology screening in most women. As part of the Choosing Wisely campaign, the American College of Obstetricians and Gynecologists recommended that routine annual cytology not be performed in average-risk women aged 30 to 65 years because "annual cervical cytology screening has been shown to offer no advantage over screening performed at 3-year intervals."[14] In 2017, an ASCCP Choosing Wisely recommendation discouraged the performance of annual cervical cytology of immunocompetent women with a history of negative screening, stating that "there is a slight increase in cancer risk by increasing the interval between screens. However, this risk is balanced with potential harm from more colposcopy as a result of spurious HPV infection that, in most women, will clear spontaneously and is unlikely to progress to any clinically relevant cervical disease."[14]

What is the actual difference in cancer reduction conferred by these 2 screening strategies? Up front, we must acknowledge that defining a precise number is challenging because of the absence of direct evidence; we must rely on model-generated estimates. These estimates vary, however, due to differing assumptions regarding the age to begin screening, age to end screening, cytology method used (conventional or liquid-based), threshold for colposcopy (atypical squamous cell of undetermined significance/HPV positive or low-grade squamous intraepithelial lesion [LSIL]), and time-delimited transitional probabilities from noncancerous states to cancer. As a consequence, the reported difference in cancer reduction between annual screening and triennial screening varies widely from 2%[15] (90% vs 92%) to 10%[16] (81% vs 91%) and to as high as 15%[17] (61% vs 76%). Notably, the absolute value of the protection afforded by annual cytology also varies widely (76%–92%). Which is correct?

Estimates with large differences in cancer protection between these 2 screening strategies have caused concern and provide the basis for the argument against using triennial cytology testing as the benchmark for benefit. However, not only is it difficult to define the absolute value of the "annual cytology" benchmark, it is more difficult to defend it as a rigid threshold within a dynamic screening process. Here is why.

Screening involves a complex balance of value-laden benefits and harms. If we make efforts to standardize a benchmark for lifetime benefit, we should equally strive to set a benchmark for lifetime harms. What should this benchmark include and what should it be? As the moderator notes, the historical standard for colposcopic referral has been at a cytologic threshold of LSIL. Should the harm benchmark, therefore, be defined by clinical algorithms set when clinicians were advised to only perform colposcopy in women with LSIL or worse cytology? For the last decade, there has been a rapid expansion of indications for colposcopy and surveillance, due to numerous combinations of minimally abnormal tests, most of which are poor predictors of underlying high-grade dysplasia or cancer. We must consider how our historical benchmark for harms has moved untethered over time and whether it too should be rectified and fixed.

As screening frequency increases, screening harms increase. Outcomes tables have focused on a few surrogate measures of harm, largely colposcopies, and false-positive testing, but the life disruptions conferred by the screening process, including extended surveillance for women with minimally abnormal results, go largely unmeasured. The small benefits gained in terms of cancer protection are offset by relatively large increases in unnecessary procedures, oversurveillance, and overtreatment. This observation underlies the argument in support of triennial testing as opposed to annual testing. The debate should be more about the net benefit of screening (defined as benefits minus harms) rather than the absolute value of only 1 side of the equation (the benefit).

Among the 4 currently recommended screening strategies in the US—and the dozen or so more HPV-based strategies on the horizon—how can we identify those that strike the right balance between benefits and harms (provides the higher net benefit)? Perhaps a reasonable metric would be the quality-adjusted life-year, a single value that incorporates both benefits and harms. Quality-adjusted life-years also have the advantage of incorporating patient preferences into the screening process by providing a patient-derived weighting factor for both benefits and harms. They also play a vital role in determining healthcare value with which other medical interventions can be compared.

However, there are other changes underway that may profoundly change the screening paradigm. Widespread HPV vaccination has the potential to reduce cancer risk to such a degree that screening intervals can be substantially lengthened, thereby minimizing harms. In a recent analysis, several current and potential screening strategies among vaccinated women conferred 90% or more reductions in lifetime cancer incidence, decreased lifetime colposcopies, and were cost-effective.[18]

Finally, it must be acknowledged that even if we were to have more precise estimates of benefits and harms, the judgment about the optimal balance between the two may change depending on the perspectives and values of those considering the evidence. This judgment has traditionally been done in style of BOGSAT (Bunch of Old Guys/Gals Sitting Around a Table), but we have done little to solicit the informed opinions and preferences of women to whom screening will ultimately be applied.

Such undertakings are time-intensive but can be illuminating. In New Zealand, for example, 11 women aged 40 to 49 years participated in an jury-style exercise in deliberative democracy to answer an important policy question: Should the New Zealand government offer free screening mammograms to women of their age?[19] All answered "yes" until they were provided actual evidence about the benefits and harms of screening beginning at the ages of 40 years versus 50 years. At the end of the 2-day deliberation, 10 women changed their minds and recommended that screening begin at the age of 50 years instead of the age of 40 years. It is intriguing to imagine what conclusions women might draw if similarly informed about expected benefits and harms of various cervical cancer screening approaches.

Should triennial or annual cytology screening provide a benchmark for reductions in cervical cancer incidence? It is obvious that establishing such a benchmark is challenging, especially if applied only to the benefit side of the screening equation. Although it may be worthwhile to consider how and if a consensus benefit benchmark may be derived, it only seems worthwhile if a harm benchmark is established as well.

Rebuttal by Dr. Kinney

Dr. Sawaya and I seem to be broadly in agreement that all of the models say that lifetime cancer risk is not the same between annual and triennial Pap screening, that recommendations from "BOGSAT" do not necessarily impact clinical practice, and most importantly that the population risk of cervical cancer is falling

because of HPV vaccination, and therefore, less intensive screening will be justified as cancer risk falls.

Our most important disagreement concerns how the newer recommendations might be crafted so that they are actually implemented in clinical practice. As a veteran of both successful and unsuccessful campaigns to chance screening methods and intervals, it is clear to me that the new recommendations must reflect the interests and preferences of the patient and providers who will need to implement them or they will be ignored (as recently demonstrated yet again). The ability for providers to assert to their patients that the new recommendations do not compromise cancer protection compared with previous practice (judged by observational data on cancer risk at intervals after a single negative test) would go a long way to motivate acceptance of the new recommendations that will surely be forthcoming. Likelihood of clinical implementation is not hard to measure: Any screening recommendations that female OB/GYN providers would not widely accept for their own medical care is "dead on arrival."

Rebuttal by Dr. Sawaya

Dr. Kinney makes important points concerning the downsides of adopting screening strategies designed to decrease screening harms that may concurrently increase cancer risk. His comments recall trade-offs that US guidelines have already made with regard to managing women with positive HPV tests and treating women with CIN 2. To decrease excess colposcopies, current guidelines recommend surveillance, not colposcopy, in women with normal cytology and a positive HPV test. To avoid potential adverse obstetrical outcomes, guidelines recommend deferring treatment of young women with CIN 2.

Of note, high-quality trial evidence demonstrates that such recommendations may lead to an increased incidence of cervical cancer. In the New Technologies for Cervical Cancer screening study, 47,001 women aged 25 to 60 years were enrolled in a 2-phase randomized trial comparing liquid-based cytology plus HPV testing (co-testing) to conventional cytology alone.[20] Colposcopy was performed in all women aged 35 to 60 years with positive HPV tests, and treatment was performed in all women with CIN 2, regardless of age. This relatively aggressive protocol led to a statistically significant decrease in cervical cancer incidence in the co-tested group.

If a major goal of screening is maintaining the highest demonstrated level of cervical cancer prevention afforded by screening, why aren't we more aggressive in our triggers to colposcopy among HPV-positive women and in our treatment of CIN 2? Because minimizing harms is important, a belief is shared by all major groups that make guidelines.[21,22]

Many will be surprised by, and disagree with, Dr. Kinney's assertion that "Neither patients nor providers consider colposcopy to be a 'harm.'" A recent systematic review summarizing 23 published reports concluded that colposcopy and related procedures cause adverse psychological outcomes, including anxiety, distress, and sexual dysfunction.[23] Even if there was no direct scientific evidence implicating colposcopy alone in such life disruptions, all busy front-line colposcopists can readily name specific patients within their own practices for whom colposcopy is a major stressor. Discounting the experiences of women does little to advance us toward forward-thinking, patient-centered models of care.

Professional societies such as ASCCP play a vital role in devising and promoting improved algorithms that navigate the tenuous (and perennially contested) lines between benefits, harms, and costs. In our health system's transition toward high-value care as it relates to multiple health conditions, it will be vital for such societies to lead the way in defining what constitutes high-value cervical cancer screening. Otherwise, they may find themselves following what others have defined for them.

Summary

Rebecca B. Perkins, MD, MS

How should we decide the standards for cancer prevention to maximize benefits and minimize harms? Dr. Kinney states that women and providers perform screening for the purpose of preventing cervical cancer, therefore maximizing prevention should be the primary consideration. He further makes the point that recommendations that are not perceived by providers and patients as maintaining historical standards of cancer prevention are poorly adopted in practice. Dr. Sawaya maintains that harms of colposcopy and other downstream consequences of screening should be considered in addition to cervical cancer prevention when designing guidelines. He notes that compromises were made in creating current guidelines to balance benefits and harms. Both Dr. Kinney and Dr. Sawaya agree that new guidelines should represent an advancement in science, considering new technologies and best practices as well as the needs of providers and women. We are on the cusp of a new era in prevention, with the potential for near elimination of cervical cancer with the right combination of vaccination and screening. Change is never easy but, in this case, is inevitable. A deliberate process that fosters consensus between front-line providers, patients, and professional organizations on which risks of precancer should prompt referral for colposcopy or other clinical actions will be crucial to widespread adoption of new guidelines.

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