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Cervical Cancer Screening Updates: The Benefits of Co-Testing

Dr. Mackey:

Welcome to a special addition of **Advances in Women's Health**. I am your host, Dr. Amy Mackey. Joining me today is Dr. Mark Spitzer. Dr. Spitzer is Professor of Obstetrics and Gynecology at the Hofstra North Shore School of Medicine, past President of the ASCCP, and Founder and Medical Director of the Center for Colposcopy in New Hyde Park, Long Island. He and I are going to discuss cervical cancer screening updates including the current Concensus Guidelines, the interim guidance on HPV primary screening, and the latest data on cytology in HPV cotesting. Dr. Spitzer, welcome to the program.

Dr. Spitzer:

Thank you.

Dr. Mackey:

Dr. Spitzer, to get us started, what are the current cervical cancer screening guidelines and how did we get there?

Dr. Spitzer:

Well, prior to 2012, we were in the Wild West of cervical cancer screening. There were competing guidelines from the American Cancer Society, the US Preventive Services Taskforce, the USPSTF, and many other smaller organizations. Providers basically did whatever they wanted and most of them did annual Paps. Then, in 2012, the ASCCP, the American Society for Colposcopy and Cervical Pathology, along with the American College of Pathology, and ACOG, and many other smaller organizations, organized a Concensus Conference to try to unify the guidelines. At exactly the same time, virtually exactly the same day, the US Preventive Services Taskforce had their own meeting and came up with virtually identical guidelines. And these are the guidelines: First of all, screening should not happen before the age of 21. At that age there is potential harm, significant potential harm, and negligible benefit. In women who have a negative screening history, you should stop screening at the age of 65, or following a hysterectomy for benign disease, and you should not resume screening even if the woman has a new partner. Between the ages of 21 and 29, cytology should be done every 3 years. You don't want to do HPV testing at this age. It's too sensitive, would detect too many low-grade lesions, but it can be used as a reflex test. Between the ages of 30 and 65, you can continue to do cytology every 3 years, that's acceptable, or the preferred approach would be to do Pap plus HPV co-testing every 5 years. And finally, the Concensus Conference found insufficient evidence to use HPV as a stand-alone screening test.

Dr. Mackey:

So, by that account it seems like we are looking at the end of the annual Pap test. Is that a fair assessment for why it wasn't included as a screening option in the new screening guidelines?

Dr. Spitzer:

Well, the individual Pap test has very low sensitivity. It's really not a very good screening test. The reason that it works and it has worked very well, is because it is part of an organized screening program of annual cytology and in that sense it has stood the test of time. In fact, Pap tests, annual Pap tests in the 20th century, are the major reason why the cervical cancer rate has dropped so dramatically. The problem is not what Pap tests miss, but what it finds. Mixed in with the high-grade lesions that we want to find are many low-grade lesions with no pre-malignant potential that will regress on their own. In fact, even 20% of CIN 2 lesions regressed within 1 year and as many as 50% regressed within 3 years. And, in fact, for every low-grade lesion identified, and that includes the CIN 2 lesions that will eventually regress, you have harmed the patient by putting the patient on the colposcopy treadmill. That treadmill of colposcopies, biopsies, and extra screenings at minimum, will cause significant psychological distress and, if you treat those CIN 2 lesions that were destined to have regressed on their own in a reproductive-age woman, you are certainly harming the patient. By extending the screening interval, you can have a negative screening test; the woman can develop a benign lesion and have it regress on its own before the next negative screening test, and the healthcare provider, the woman herself would be no wiser, would have no idea that she had this benign lesion, and there would be no decrease in protection because that lesion had no pre-malignant potential and because she had a subsequent negative screening test. But the key to that 5-year extended screening interval is the sensitivity of the HPV test. Because it detects disease so early in what is actually a very long carcinogenic process, its sensitivity is equivalent to the annual Pap test.

Dr. Mackey:

So, is that the final word? Is there a consensus here?

Dr. Spitzer:

Well, in 2014 we had the ATHENA trial. The ATHENA trial was the pivotal trial to the cobas HPV test. And what it did was it looked at stand-alone HPV screening at 3 year intervals beginning at the age of 25. And the study went something like this: There were 42,000 women and they looked at 3 different screening strategies, each at 3 year intervals. There was cytology alone. There was HPV primary screening but with genotyping in women over the age of 25. And then, there was the hybrid strategy that was represented as the current screening recommendations, and in that strategy they looked at cytology alone in women 25 to 29, and co-testing but without genotyping in women over the age of 30. The conclusions of the ATHENA trial was that HPV primary screening in women over the age of 25 is always more effective that cytology alone, we'd expect that, HPV testing is more sensitive than cytology, but also that it was as effective as the hybrid screening strategy, but because HPV primary screening required fewer screening tests, it was more cost effective. Based on that trial, the FDA in 2014 approved primary HPV screening and in 2015 the ASCCP published interim guidance for HPV primary screening in women over the age of 25. And the screening guidance looks something like this: You can screen women every 3 years with the cobas HPV test, the only one that has FDA approval for primary screening with HPV, and it looks at 14 different genotypes. If the patient is positive for HPV 16 or 18, she gets immediate colposcopy. If it's positive for one of the other 12 types, she gets reflex cytology; sort of the reverse of what you get with ASCUS Pap test where you have reflex HPV testing, this would be reflex cytology. And if you are positive for ASCUS or anything worse than that, you get colposcopy. On the other hand, if you have a negative cytology you get followup 1 year later with another screening test. If you are negative for HPV you would not be rescreened until 3 years later as a routine.

Dr. Mackey:

So if HPV primary screening is just as good as co-testing, do we still need Pap tests?

Dr. Spitzer:

Well, the truth of the matter is that the conclusion of the ATHENA trial is actually a little bit misleading. There's no question that at 3 year intervals, HPV primary screening will detect more CIN 3+ lesions than cytology alone; that's for sure. But the authors represented the hybrid strategy as mimicking current US screening guidelines. But the hybrid strategy didn't include genotyping while their HPV primary screening did. And current guidelines clearly include HPV 16/18 genotyping in the recommendation. You ask yourself, "What's the big deal whether you do genotyping or don't do genotyping?" Well, since about half of the CIN 3+ lesions in the ATHENA study were HPV

16 or 18 positive, HPV primary screening had those patients get immediate colposcopy while the hybrid strategy had to wait 12 months for repeat co-testing before they got the indication for colposcopy, and during that interval many of these women were lost to followup. And by losing these women to followup and not detecting CIN 3 lesions, there were in fact fewer CIN 3 lesions in the hybrid strategy than there were in HPV primary screening. If you wanted to conclude properly from the ATHENA trial, the correct conclusion would have been that HPV primary screening with genotyping is as effective as hybrid screening without genotyping. This would put a completely different spin, however, on the conclusions.

Dr. Mackey:

If you are just tuning in, this is Advances in Women's Health. I am your host, Dr. Amy Mackey and I'm joined by Dr. Mark Spitzer with the Center for Colposcopy in New Hyde Park, Long Island. We're discussing the role of stand-alone HPV testing and co-testing in cervical cancer screening.

So, Dr. Spitzer, what other new information is out there that would help us clarify the benefit to cytology.

Dr. Spitzer:

In 2015, Amy Blatt and her colleagues published the *Quest Diagnostic Experience with Cervical Cancer Screening*. It was a flawed study in that it was a real-world study that lacked rigorous followup. In other words, not all of the patients who had their screening test done at Quest had their followup biopsy done at Quest. Nevertheless, the study deserves our attention because it was huge. Over 8.6 million women, over 250,000 biopsies, and over 500 cases of invasive cervical cancer. To get a sense of the scale, that's over twice as many as Kaiser Permanente Northern California. And Kaiser Permanente Northern California was considered so large that we based practically our entire guidelines for the management of women with abnormal Pap tests on that study alone. The study went something like this: They looked at the histology within 1 year of a Pap plus HPV co-test screening and this allowed them to look at the results of the histology based on 3 screening protocols: Pap alone, HPV alone with Hybrid Capture 2 as the HPV test, and Pap plus HPV co-testing. And this is what they found: HPV alone missed 6% of the CIN 3 lesions; Pap alone missed 8.7% of the CIN 3 lesions; while cotesting missed only 1.2% of the CIN 3 lesions, but the real exciting information comes from the information on invasive cancer. With invasive cancer, HPV alone missed 18.6% of the invasive cancers; Pap alone missed 12.2%; while co-testing missed only 5.5%. For any of you who are paying attention, this is a very striking result and might be confusing because of our notion that HPV testing is a much more sensitive test than cytology. How is it then, that HPV missed more cases than cytology? The answer might come because the benefit of HPV testing is primarily in the early detection of pre-cancer. As lesions become malignant and therefore less differentiated, viral loads become lower and may drift below the test cut-off point for positive tests. Other items that lower the viral load are old age and adenocarcinoma. In fact, in this study, 27% of adenocarcinoma was HPV negative. The authors also extrapolated the results to the US population and they estimated that up to 20% of women in the United States diagnosed with cervical cancer each year could be misdiagnosed if they were screened with HPV alone.

Dr. Mackey:

And was this study enough to justify co-testing?

Dr. Spitzer:

Not by itself. The study, as we said, was a retrospective real-world study. In order to draw firm conclusions you needed the study to be more rigorous; in other words, to have better followup on the screening tests. The major strength of this study was the fact that it was so large; however, Kaiser Permanente Northern California was an also very, very large study, and it reported on a captive HMO population where they did have strong followup and therefore were able to draw a conclusion. And KPNC found less cancer and less CIN 3+ three years after a negative co-test, than after a negative HPV test. Same as Quest. Taken together, these 2 huge studies point in the same direction, namely, that co-testing at 3-year intervals is a better screening test than stand-alone HPV testing.

Dr. Mackey:

So, with the backing of those 2 studies moving along the same direction, does that become the final word on the Consensus Guidelines?

Dr. Spitzer:

Not quite. I have one final thought. Earlier this year, several thought leaders including Walter Kinney who is thehead of Kaiser Permanente Northern California, Tom Cox, former President of the ASCCP, Tom Wright, also a former President of the ASCCP and the lead author on the ATHENA trial, and Warner Huh, who is the lead author of the *Interim Guidance for HPV Primary Screening*, and you can include me in this sentiment as well, authored an opinion piece published in the *Green Journal*. They questioned the cost-benefit trade-off of increasing the co-testing interval from 3 years to 5 years. Specifically, they noted that by increasing the intervals from 3 to 5 years, it would result in an increase of 2.7 cases of cervical cancer and 0.6 cases of cervical cancer deaths for each 1000 women in the United States, aged 30-64, at the cost of about 250 extra colposcopies. And here, by cost, you have to understand that they mean the harm. They measured harm in the sense of number of colposcopies. Moving back from 5 year co-testing to 3 year co-testing would cost 92 extra colposcopies and 3.2 extra LEEPs for every case of cervical cancer prevented and 409 extra colposcopies and 14.3 extra LEEPs for every preventable death. Furthermore, in the United States, we do not have an organized screening program. What we have is an opportunistic screening system. And the authors asked a very cogent question, is a 5-year interval really safe without a computerized call/recall system to get women back at 5 years? How do we know they're going to come back at 5 years? Without an organized system, 5 years could become 6 years, or 7 years, or 8 years, or even more, and there's no evidence that that interval is safe. The guidelines assumed that women would comply and preventing a few extra cancers and deaths was not worth the harm as measured by the extra colposcopies and LEEPs, but it's not clear that the medical community, in general, or women as a whole share that judgment. As a matter of fact, in the very same issue of the Journal, I think it was the very next article, there was a survey of over 500 women in the HPV and Perimenopause study. In this study, 50% of the women were aware of the changed guidelines and 75% still believed in annual screening. Two-thirds were willing to extend from their annual screening to 3 years if it was strongly recommended by their doctor, but only 25% would extend it all the way out to 5 years. Sixty percent had a strong preference for Paps and 40% had at least a moderate concern about HPV primary screening.

Dr. Mackey:

Before we wrap up, Dr. Spitzer, are there any parting comments you want to summarize for our audience?

Dr. Spitzer:

Sure. HPV testing is more sensitive than the Pap test; that's clear. Annual Paps in an organized screening program work very well at detecting pre-cancer and preventing cancer, but, and this is a very big but, it detects many lesions with no premalignant potential whose evaluation and possible treatment harms the patient. HPV testing, at greater intervals, allows many transient lesions to regress on their own without being detected, while true premalignant lesions would be detected early enough in the process to prevent cancer, despite the extended screening interval; however, as the Quest study shows, and KPNC confirms, co-testing still has a significant role to play in cervical cancer detection and prevention. Possibly because higher grade lesions produce less HPV or because of age or because of adenocarcinoma, stand-alone HPV testing is not as sensitive as when it is combined with cytology in co-testing. The Quest study estimated that as many as 20% of cancers in the United States may be missed with HPV-only screening. Finally, the jury is still out on the move to 5-year screening intervals. It's not yet 5 years since the screening guidelines were published; that would be 2018. So, we don't know the effect that this change may have, but there are some prominent voices that are starting to come out questioning the trade-off that was made by extending the screening interval to 5 years. The evidence clearly shows that 3-year co-testing is the most sensitive screening option currently available and may represent the most acceptable balance between benefits and harms to the medical community at large, and to women as a whole.

Dr. Mackey:

Well, with that, I want to thank Dr. Spitzer for sharing his thoughts with us about cervical cancer screening. Dr. Spitzer, thanks again for joining us.

Dr. Spitzer:

Thank you.