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https://reachmd.com/programs/cme/primary-high-risk-hpv-testing-clinical-practice/8010/

Released: 05/17/2016
Valid until: 05/17/2017
Time needed to complete: 15 minutes

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Primary High-Risk HPV Testing in Clinical Practice

Narrator:

Welcome to CME on ReachMD. This segment: **Primary High-Risk HPV Testing in Clinical Practice**, is sponsored by Omnia Education and supported by an educational grant from Roche Diagnostics.

Dr. Caudle:

While the prevalence of cervical cancer in the population has decreased over the years, there are still 12,990 new cases and 4,120 deaths estimated in 2016; however, in spite of this progress, there is marked uncertainty among healthcare providers regarding the optimal screening strategy for cervical cancer. While both primary high-risk HPV testing and cotesting approaches are known to be superior to cytology-alone approaches, current evidence indicates that patients as well as providers continue to favor cytology-based testing annually. Healthcare providers thus face challenges in integrating cotesting and primary high-risk HPV testing in clinical practice, or choosing one over the other for individual patients.

I am your host, Dr. Jennifer Caudle, and joining me today is Dr. Warner Huh, the Margaret Cameron Spain Endowed Chair in Obstetrics and Gynecology. He is also Professor and the Division Director of Obstetrics and Gynecology at the University of Alabama at Birmingham in Birmingham, Alabama. Dr. Huh, welcome to CME on ReachMD.

Dr. Huh:

Thank you for having me. It's a pleasure to be invited.

Dr. Caudle:

So, let's get started. Dr. Huh, let's first discuss what primary high-risk HPV testing is and why this is clinically important.

Dr. Huh:

Well, what primary high-risk HPV testing is simply, is there are 14 types of HPV, or the human papilloma virus, and this is a virus that is known to be causally related to cervical cancer and, more importantly, what we know is that the vast majority of cervical cancers, both in the United States as well as worldwide, are directly associated with high-risk HPV. So, over the last decade or so, what we have recognized is that the high-risk HPV test, the DNA test, can be used to screen women for cervical cancer and during that same time period what we've also learned is that the Pap smear, something that's really been around since World War II, really may, in fact, may not be that great of a screening test. The false-negative rate or the sensitivity for a Pap smear is about 50%. So, in reality, we wind up missing a lot of clinically significant disease or cancer or precancer when we use Pap smears or cytology by itself. Now the consequence, as we've learned more about the relationship between HPV and cervical cancer and the limitations of Pap smears, this… sort of this incredible intersection and recognition that we can use high-risk HPV testing, or primary HPV testing, as a screening modality for women for the prevention of cervical cancer.

Dr. Caudle:

So, is primary testing meant to replace the Pap smear? And you did mention some of the limitations of continuing Pap smear screening, can you discuss other limitations that might exist as well?

Dr. Huh:

So, no, the primary HPV screening is not meant to replace the Pap smear. I think there's a lot of misunderstanding that all of a sudden that we're going to create this/use this test and that Pap smears are going to go away. The way it's currently recommended, both by a couple of professional societies as well as the Food and Drug Administration, is that we're actually going to, instead of using the Pap smear first, and let's say the high-risk HPV test second, we're essentially going to flip the order. So, instead what we're going to do is use the HPV test first. If it's abnormal or you have certain abnormalities, then you would triage to a Pap smear. And there are a couple of reasons why this is important. One of which is that whenever you screen for a test, whether it's for cancer or anything else, you want to use the test with the best sensitivity, or the lowest false-negative rate, and that's what the high-risk HPV test does, exactly does, it actually has an extraordinarily high sensitivity, a sensitivity in the high 90s. What's good about the Pap is that even though it has a lower sensitivity or higher false-negative rate, it actually has a much better specificity or lower false-positive rate. And so what we've done, effectively, by changing the order is use the better test first and then use the better triage test second, i.e. cytology or Pap smear screening. And this is how we screen for other diseases. This is how we screen for things like HIV and syphilis. We always use the more sensitive test first. But, you know again, what's really important for women is to be able to tell women if they have a negative test, and in this circumstance a negative high-risk HPV test, that, in fact, genuinely that they really have a negative test and their risk of developing precancer or cancer is extraordinarily low. And I think that's really the main message here is the value of a woman recognizing that there test is genuinely negative and what those clinical ramifications are.

And I think in regards to the second part of your question about continuing a Pap smear screening, my biggest fear is this: We know that Pap smears miss a lot of disease, but as more women and girls in this country get vaccinated against HPV, disease prevalence, or the rates of these diseases will plummet. And we know they will plummet because in countries like Australia, where they have extraordinarily high rates of HPV vaccination, they're already seeing 95% reductions in things like genital warts, which are also directly related to HPV. If you continue to use Pap smears in that screened population, a population that is vaccinated, you're going to wind up missing a huge amount of disease. And this is the perfect time for us to be able to find a replacement screening test. There's no question that the Pap smear has done its job. It has done its job extraordinarily well over the last 50 or 60 years, but what we're recognizing today is that maybe we've hit the glass ceiling, so to speak, with cytology or Pap smears as an effective screening test.

Dr. Caudle:

Thank you very much. Now there seems to be continued emphasis on cotesting in the most recent screening guidelines from the American Cancer Society and treatment guidelines from the American Society for Colposcopy and Cervical Pathology. So, what is cotesting and why is this important?

Dr. Huh:

Well, what cotesting is, by definition, is the combination of a Pap smear and an HPV test that is done simultaneously. Not sequentially, but at the exact same time. So, in the United States, there are numerous professional societies, as well as the United States Preventive Services Task Force that recommends cotesting, Pap plus HPV, starting in women 30 years and older. The question is: Why? And the reason why is that having this backbone of an HPV test that's added to cytology or Pap smears greatly improves the screening efficiency of those two tests. And what we know is that a women who has a negative Pap as well as a negative HPV test, that woman's at an extraordinarily low risk of developing cervical cancer over at least a 3 to 5 year window. Okay? And so, again, it really kind of portrays a very strong negative predictive value message for women who have those results. More importantly, in the 15% of women that might have an abnormal test combination, particularly one that has a positive HPV result, what we know is that really does trigger an additional evaluation that really is worthwhile for those women. But basically the reason we added it, it's kind of the same message that I talked to you earlier about, primary HPV, there is really a very strong predictive value of adding an HPV test to a Pap smear and that's why multiple groups across the US, as well as worldwide, have really espoused the value of cotesting.

Dr. Caudle:

Thank you for that. Is there any clinical value at looking at specific genotypes of HPV to determine if some women are at lower or greater risk for cervical cancer?

Dr. Huh:

As I mentioned earlier, there are 14 high-risk or genotypes of HPV that have been directly associated, epidemiologically, with the development of invasive cervical cancer. So, when we say genotypes, these actually represent the individual types of HPV that we look

at. So, there are actually two types and the two types are: Type 16 and type 18. I want to spend a little bit of time talking about type 16 and why type 16 is really important, clinically. First off, type 16 is by far the most prevalent or the most common type that we see in the US and worldwide. Secondly, the problem with type 16, it's actually the most virulent, or the worst actor of all the types. It's the type that's associated with the highest risk of developing disease. And so, for the audience and listeners, what's really important to recognize is, we're not so much concerned about a woman getting that one-time HPV infection. What we're concerned about is this concept of persistent HPV infection, having an infection or an infection with a genotype like 16 over an extended period of time, whether it's 12 months, 18 months, or 24 months. And so, there have been several studies that have been done, both in the US and worldwide, that demonstrate a woman's lifetime risk of having a persistent HPV 16 infection, of getting something like CIN 3 or severe cervical precancer, is as high as 30 to 35%. And if you take a step back and think about it, there's very little in women's health that carries a risk that high; so, that's a pretty substantial risk. And so, what we have learned is that by teasing out specific genotypes, we can actually sort of stratify management and evaluation by this concept of risk. So women who are at higher risk might need an intervention that's sooner or more aggressive than a woman that's at lower risk. The other type I talk about, type 18, is more classically associated with what we know adenocarcinomas of the cervix which are slowly on the rise; they're harder to detect, cytology doesn't do a very good job of detecting these, and that's why type 18 is actually of interest to the US screening population as well. But there's no doubt in my mind that there is a very specific clinical value to testing for specific genotypes, particularly type 16 and type 18. And to take that one step further, we actually already have incorporated that into our primary HPV screening algorithms, the value of teasing out these genotypes in terms of those women who are 16 or 18 positive, well, those patients probably need an evaluation much sooner than those who are not positive for type 16 or type 18.

Dr. Caudle:

Thank you for that. Dr. Huh, why is the screening interval so long in women who are HPV-negative and Pap-normal?

Dr. Huh:

Well, I guess when you ask me the question, why's is so long, I mean, the current recommendation is that in women who are Pap negative and HPV negative, that they be screened every 5 years. So, I guess, for some people that is really long and, personally, as a clinician and provider, I agree. I think it's really, really long. I think it's too long, in fact. But the reason it's so long is that based on modeling studies, people have demonstrated that, again, that the risk of developing cervical cancer or even cervical precancer, it's extraordinarily low and the value of screening more frequently than that is not there, at least from a public health perspective. Here's the problem that I have with it, and I look at it from a very pragmatic or practical perspective. So not so long ago, 5 years ago, in fact, we were screening women every year and that was the norm and that was the understanding both from providers and patients. And so, to go from 1 year to 5 years, in my opinion, is a quantum leap. We simply don't have the mechanism in the United States for patients and providers to remember how often patients have been screened, when their last screening test was. Here's my other concern. I personally don't remember what kind of healthcare I received 5 years ago and that's probably true for many Americans in the United States, but what happens if 5 years becomes 6 years, or 7 years, or 8 years? Because what we do know is that as every year goes by, the individual risk for a woman for developing cervical cancer does increase incrementally, and so, my concern is that what if women forget about screening 5-years-plus out. Are we actually potentially harming women by creating an interval that's way, way too long? And so, in some ways, I feel that it's sort of an issue that needs to be re-visited by the screening societies or the societies that make screening guidelines, and other people feel that it's an appropriate interval, but right now it's set at a 5-year interval for women 30 years and older.

Dr. Caudle:

Thank you for that. Well, let's switch gears here and talk about screening. Why do most women in the United States, who have cervical cancer, continue to be unscreened or under-screened?

Dr. Huh:

Well, it's an interesting question. So, what we've known, and there's an original report that was published by the NCI in the late '90s that demonstrated that roughly 50% of women in the United States who have cervical cancer have been completely unscreened and about another 15 to 20% who have not been screened in the last 5 years. And I think it's important to recognize that that's really old data. I mean, that's data from the mid '90s and it's based on fairly small reports and so, even in 2016, I don't think we have a true handle on the number of women in the United States who have invasive cervical cancer who have been under-screened and unscreened. What we do recognize is that there's no question that that is a risk factor. We know that women who are under-screened -- there are very few women who are unscreened -- but women who are under-screened are definitely at risk for developing cervical cancer. But, you know, I think the more important thing, and the CDC put out a report a couple of years ago on this, roughly 7 out of 10 women who are not appropriately screened actually had health insurance and access to a provider. And so one thing, I think, that we're recognizing is

maybe there's a good chunk of women in the United States who have cervical cancer who are not so much under-screened or unscreened, but they're not screened appropriately by their provider. And so we're actually looking at this actively with multiple groups and trying in terms to understand why women get cervical cancer in the United States, but what has been classically taught is that, if you're under-screened or unscreened, you're definitely at risk, which is why the screening message is still very much important in 2016.

Dr. Caudle:

That's great. Let's talk about women who have been vaccinated against HPV. Do these women still need to be screened for cervical cancer?

Dr. Huh:

The simple answer to the audience and the listeners is absolutely yes. In 2016, women who have received the HPV vaccine, or girls who have received the HPV vaccine, still absolutely need to be screened. Our patients and providers must not have this belief that because they've been vaccinated that they're protected against cervical cancer, all kinds of cervical cancer, for their entire life. They absolutely need to be screened. The bigger question is, do they need to be screened differently? And we don't know that; we don't really have guidelines or enough data to demonstrate that women who have been vaccinated can be screened less frequently or less aggressively. So, the answer to your question is that women absolutely need to be screened, but what I think you're going to see in the next decade or so is that we very well may have recommendations that stratify women who have been previously vaccinated and those women that have been vaccinated may, in fact, may need to be screened less frequently.

Dr. Caudle:

That's great. The screening and treatment guidelines for cervical cancer often seem overwhelming for many of us physicians and I often feel like we actually need an app to really understand them all. Can you really comment on this and do you expect future guidelines to be even more complicated?

Dr. Huh:

I think for the listeners, I think this may be actually one of the most important questions, and as someone who is guilty of writing the most recent treatment guidelines for the ASCCP as well as contributing and helping with the development of the app that you're talking about through the ASCCP which is a fantastic app, it's a reflection of how we've incorporated all these additional studies and evidence into our guidelines and how it's made them literally exponentially more difficult to understand and embrace. There aren't just one or two choices, now there are multiple different choices. And what I fear is that, yes, to answer your question, is that there is the distinct potential of making it even more complicated in the future where you would definitely have to rely on your app more, you just can't look at an algorithm and quickly figure out what to do for a patient when you're seeing 40, 50 patients in a session. But with that being said, and this is an ongoing debate that we have amongst a lot of the experts that I work with in this arena, is that, do we need to take a step back and maybe embrace some element of simplicity? Because what I'm concerned about is, as we make it more complicated providers don't quite understand the algorithms, because they're complicated, and then what happens, inadvertently and incorrectly, is they wind up screening or treating incorrectly and wind up hurting women. And so, I think in the next several years you're going to see a big push to maybe potentially make our guidelines less complicated and more simple in the hope of really doing the right thing for women.

Dr. Caudle:

Well finally, Dr. Huh, are there any points that you would like to discuss for our learners further that we haven't addressed during our discussion?

Dr. Huh:

I think two things and they're pretty simple. One is that we should be aggressively vaccinating our daughters and sons against HPV. We have a very unique opportunity of eradicating a terrible disease that's caused by a common virus, HPV, both in the United States and worldwide, and we should be pushing for that. I think the health benefits are enormous in this country in terms of HPV vaccination. And then, secondly, providers have to recognize that screening is still very much effective in this country in terms of reducing the incidence, the mortality and the morbidity of cervical cancer, so we need to continue to screen. This is one of the few solid cancers, both in men and women and children combined, where we can literally make dramatic reductions and we have the tools to do it, but we just haven't been using them properly and I think that's what we need to really focus our efforts on.

Dr. Caudle:

Well Dr. Huh, thank you very much for your time today and for sharing your insights on Primary High-Risk HPV Testing in Clinical

Practice.

Dr. Huh:

Thank you for having me. It was an honor.

Narrator:

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