

# Cervical Cancer Screening with HPV Test

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[Dr. Saraiya] Welcome to this CDC series of programs on cervical cancer screening. I'm your host, Dr. Mona Saraiya. My guest today is Dr. Stewart Massad. Dr. Massad is a professor in the Division of Gynecologic Oncology at Washington University in St. Louis, where his academic interests focus on cervical cancer prevention and medical education. He's also a member of the board of the American Society for Colposcopy and Cervical Pathology, and was on the steering committee that developed the ASCCP's 2006 Consensus Guidelines on the management of abnormal cytology and histology. He's also an advisor to the Illinois Breast and Cervical Cancer Screening Program. Welcome, Dr. Massad.

[Dr. Massad] Thanks, Dr. Saraiya. I'm grateful for the opportunity to help clinicians better understand this vital topic.

[Dr. Saraiya] Dr. Massad, for decades, cervical cancer prevention was based on Pap testing, that is, using cytology to identify women at risk for cervical disease, finding lesions with colposcopy, and treating premalignant lesions before cancer developed. This was tremendously successful, driving cervical cancer from the leading cancer among women off the list of the top 10. What do you think is the reason cervical cancer screening was so successful?

[Dr. Massad] Pap testing with colposcopy and treatment of significant premalignant lesions has been *the* most successful program for cancer prevention because of the sensitivity of serial testing which is high and because cervical lesions progress to cancer over a time span of years to decades.

[Dr. Saraiya] And what is the sensitivity and the specificity of a Pap test?

[Dr. Massad] A single Pap test may miss up to 50 percent of significant lesions; that's a pretty scary number. But when considering ancillary tests to improve the sensitivity of screening, clinicians need to keep in mind that no one has ever advocated doing just one Pap. That means that missing an early lesion almost never leads to patient harm because the missed disease is likely to be picked up in subsequent testing. For example, women in the CDC's National Breast and Cervical Cancer Early Detection Program who had at least three negative Paps had a cervical cancer risk of only three per 100,000 over three years. With regards to specificity, it is generally very high, as is the corresponding negative predictive value suggesting that if a woman has a negative Pap test then she can be assured that she does not have disease. However, the U.S. health care system has inequities, and not everyone gets Pap tests on time. In fact, about half of all cervical cancers occur in women who aren't properly screened.

[Dr. Saraiya] As I understand it, over the past five years, screening has broadened to include the concept of cotesting with HPV as part of a cervical cancer screening program. What is cotesting and what is the sensitivity of cotesting?

[Dr. Massad] Cotesting is testing for both high-risk, or oncogenic, human papillomavirus DNA and for an abnormal Pap. Cotesting can be done with a conventional Pap test but a second swab sample is needed. With liquid-based sampling, clinicians can run both tests off a single specimen obtained at a single visit. Simultaneously testing for HPV along with the Pap improves the sensitivity of a single Pap test. We're less likely to miss disease at any one visit with cotesting than with Pap testing alone.

In contrast to Pap testing, HPV testing has a sensitivity for CIN2, CIN3, or cancer of about 90 percent. And when Pap and HPV tests are combined, the sensitivity surpasses 95 percent and the negative predictive value approaches 100 percent.

[Dr. Saraiya] What about the specificity of cotesting?

[Dr. Massad] Unfortunately, the tradeoff to better sensitivity is loss of specificity. We're more likely to find premalignant lesions, but we're also more likely to find problems that aren't real. That doesn't mean that a positive HPV test is often positive when there's no HPV, though that does happen. It means that most HPV infections don't lead to cancer. It's hard to know just what specificity is, as reports vary substantially. For example, older women have a lower prevalence of HPV and so a greater specificity with HPV testing. Some of the problems with the reported studies include short duration, different cervical disease endpoints, and a positive HPV test managed with colposcopy even when the Pap was negative. Also, many of the studies were sponsored by corporations that sell HPV tests, raising the possibility of bias. But to answer your question, the specificity of the Pap test alone is about 85 percent, while the specificity of HPV testing is around 75 percent, and that of cotesting is lower still. Since most women don't have disease, that means that cotesting often misidentifies women. They may have HPV DNA, but they don't have precancerous cervical disease.

[Dr. Saraiya] The guidelines say that combining the Pap test with the HPV DNA test can allow clinicians to extend the screening interval to at least three years if both tests are negative. What's the rationale behind this?

[Dr. Massad] Excellent sensitivity and negative predictive value mean that women with negative cotesting results have minimal risk of developing disease over three years—less than 1 percent will develop CIN3 or cancer.

[Dr. Saraiya] Wow. Clinicians may want to do both tests every year. Should they?

[Dr. Massad] Testing more often doesn't improve the low risk. Many women with HPV — including most women with high-risk HPV infections — will clear their HPV infections. Once that happens, cancer risk is minimal. And this isn't true just of HPV infections. Most CIN1 lesions and up to half of all CIN2 lesions will clear without any treatment. So finding HPV or lesions that are destined to disappear doesn't help patients. It just adds to their anxiety and cost. One way to balance the tradeoff between sensitivity and specificity is to screen less often with cotesting. That way, newly acquired HPV infections and low-grade cervical lesions have a chance to regress, and we're much more likely to find persistent lesions, which have a much higher risk of eventually progressing to cancer.

[Dr. Saraiya] Well Dr. Massad, what about just doing the HPV DNA test without the Pap?

[Dr. Massad] HPV testing has been proposed as a stand-alone screen to replace the Pap test, and there are interesting studies being done that may lead us in that direction, but it is not currently FDA approved for that indication. Also, HPV rates are very high in women before age 30, so the specificity of HPV testing in young women is insufficient to allow its use in that group. Employing one screening modality — cytology — for young women and another — HPV testing — for older women may confuse women and clinicians. For now, we're sticking with Pap testing, alone or as part of cotesting.

[Dr. Saraiya] How do you feel about cotesting in your practice?

[Dr. Massad] Well, as someone who cares for indigent women with a lot more immediate things to worry about than whether they'll get cancer in a decade or two, and so may not return regularly, I find that the added sensitivity that comes from combining the HPV test with the Pap is attractive.

[Dr. Saraiya] Dr. Massad, can you provide guidance on who is an appropriate candidate for cotesting? For example, if a woman has a history of abnormal Paps in the past but is on a normal screening cycle, would she be an appropriate person to cotest and possibly extend the screening interval?

[Dr. Massad] The science suggests that all women over 30 who haven't had a hysterectomy are good candidates for cotesting and three-year screening, including women more than a year out from treatment of CIN. In applying cotesting and three-year screening, clinicians should work to ensure that appropriate reminder systems are in place; it's harder to remember a three-year cycle than an annual one. In addition, cotesting is only appropriate for those who understand the natural history of HPV - not just its role as a cause of cervical cancer, but its transience in most women. That's important for the more than 10 percent of women who will have abnormal HPV results to ensure that they don't demand testing and treatment that won't benefit most of them.

[Dr. Saraiya] ASCCP came out with new guidelines in 2006 for using the HPV DNA test as a cotest. Give us a brief overview of what the guidelines say for specific test results. Let's start with the easy one - both your Pap and HPV tests are negative.

[Dr. Massad] For women with dual negative tests — a negative Pap and a negative HPV test — retesting in three years is advised. It is not advised to do both annually.

[Dr. Saraiya] What do you do if the Pap test is abnormal?

[Dr. Massad] For women with an abnormal Pap, clinicians should follow the guideline for the Pap - colposcopy for ASCUS with a positive HPV DNA test, repeat Pap in one year for ASCUS with a negative HPV DNA test, and colposcopy for all other grades of abnormal cytology, regardless of HPV result.

[Dr. Saraiya] So, are you saying that we should send a woman to colposcopy even with a negative HPV test?

[Dr. Massad] The meaning of HPV-negative HSIL isn't clearly understood, since all true cancer precursors should be HPV-associated. But since false-negative HPV tests can occur, colposcopy is recommended as a safety measure for all women with ASC-H, Low SIL, High SIL, and atypical glandular cells or AGC. The only exception would be the postmenopausal woman with Low SIL who could be triaged for Low SIL using HPV test results as others are for ASCUS.

[Dr. Saraiya] OK. What about those women who have a normal Pap but a positive HPV test?

[Dr. Massad] The consensus at the ASCCP guidelines conference was that these women are at higher risk than women who have dual negative results, but their risk is too low to justify the cost and discomfort of colposcopy. Instead, HPV-positive / Pap-negative women should be screened with both tests in one year.

[Dr. Saraiya] Why would we wait a whole year before repeating both tests?

[Dr. Massad] Women with negative cytology are unlikely to develop cancer in the next year. Most of the HPV infections we detect with cotesting are actually transient. But HPV is cleared through cell-mediated immunity, which is a slow process. In contrast to most viruses, HPV remains in the epithelium, so dendritic cells are slow to recognize HPV infections. It can take months to clear HPV. Early testing might identify disease as persistent even when it's on its way out. It actually can take two years or more to clear HPV, but we chose a 12-month observation window to balance the risk of viral regression against the low risk that disease would progress.

[Dr. Saraiya] Why do you think providers would prefer to use the HPV DNA test as a cotest?

[Dr. Massad] The benefit of cotesting is the security of a higher sensitivity test and the convenience of extended screening intervals.

[Dr. Saraiya] Why is it that providers have seemed to adopt the HPV DNA testing but not the increase in screening intervals?

[Dr. Massad] We've been so successful over the past few decades at indoctrinating women and clinicians about the importance of annual Pap testing that it's difficult to back pedal. Many clinicians understand that every screening test will miss some cancers, and they don't want to be blamed, so they keep screening annually. Some worry that while women and office computers can mark next year's calendar, we may lose track of a three-year scheduling cycle.

Marketers have pushed cotesting as a way to improve peace of mind, but messages about longer screening intervals and the problems arising from false positive results have been much more muted. As a result, some clinicians are offering annual cotesting in a mistaken push to minimize risk. They don't understand that most of the disease they'll detect is transient and women are more likely to be harmed from overtreatment.

[Dr. Saraiya] Dr. Massad, what can you say about malpractice around this topic of increased screening?

[Dr. Massad] An unfortunate aspect of marketing has been the proliferation of opinions from otherwise respected leaders in medicine and law arguing that HPV testing has become the standard of care. That's a legal term and I'm not a lawyer, but standards for screening have been established by prestigious national associations, including the American Cancer Society and the United States Preventive Services Task Force.

These groups make clear that cytology alone remains a perfectly acceptable approach to screening, and for women over the age of 30 with prior negative tests, screening at two- to three-year intervals is acceptable. Cotesting may be attractive, but clinicians shouldn't adopt it out of fear, and they certainly shouldn't recommend annual cotesting out of fear since there are clear guidelines against doing so, and so any patient harms that result may be indefensible.

[Dr. Saraiya] Do you have any additional reassuring messages to primary care clinicians about extending the screening intervals?

[Dr. Massad] We know from several modeling studies that the benefits of annual testing with Paps alone are marginal when compared to testing at three-year intervals. We know we can never eliminate cervical cancer, no matter how often we test. We can only drive rates down at the margins. I often get a laugh at meetings by suggesting that if sensitivity for detecting CIN is the only criterion we use to judge a test, we should be giving women handfuls of cervical brushes and having them do daily self-cotesting. Even then, some cancers would occur, as some cancers appear to shed cells poorly or occur high in the endocervix where they're hard to detect. Three-year cotesting offers a nice balance between the drive for optimal sensitivity and cost-effective, evidence-based practice.

[Dr. Saraiya] Dr. Massad, what have women in your practice said about not coming in annually for a Pap test?

[Dr. Massad] Women worry about cancer and want to minimize risk but often don't understand the risks of overscreening. Treating lesions destined to regress can result in out-of-pocket costs, disrupted relationships, bleeding, and cervical incompetence. One study showed that many women thought that recommendations to lengthen screening intervals were just another gimmick designed to cut health insurers' costs. Once I talk to them about the transience of most HPV infections and the hazards of overtreatment, especially for future pregnancies, they understand. Unfortunately, it's often easier to do the test than to do the talk.

[Dr. Saraiya] Dr. Massad, thank you so much for taking the time to speak with us today. If you're interested in learning more about what Dr. Massad shared with us today, you can go to [asccp.org](http://asccp.org).

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