Expert Interviews

National STD Curriculum Podcast

HPV & Anal Cancer Screening

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Dr. Helen Stankiewicz Karita, Associate Professor at UCSF and a national expert on human papillomavirus (HPV)-related diseases in the anal canal, and National STD Curriculum Podcast Editor Dr. Meena Ramchandani discuss screening tools for anal dysplasia and anal cancer.

Topics:

- HPV
- penile cancer
- dysplasia
- anoscopy
- HRA

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Disclosures

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References

IANS Guidelines

Transcript

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introduction**[00:00] Introduction**

Meena Ramchandani:

Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STI [sexually transmitted infection] review for health care professionals who are interested in remaining up to date on the diagnosis, management, and prevention of STIs.

We are very excited to welcome Dr. Helen Stankiewicz Karita to discuss clinical updates in HPV. Dr. Stankiewicz Karita is an infectious disease physician and an associate professor at the University of California, San Francisco. And her area of focus is HPV [human papillomavirus]-related diseases in the anal canal, including primary and secondary prevention of HPV-related cancers, clinical trials of vaccines, and therapeutics for HPV-related disease. Welcome, Helen. It's so great to have you on this episode.

Dr. Stankiewicz Karita

Hi, Meena. It is a pleasure to be here. Thank you so much for the invitation.

anal-cancer-detection**[00:57] Anal Cancer Detection**

Stier EA, Clarke MA, Deshmukh AA, et al. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. Int J Cancer. 2024 May 15;154(10):1694-1702. [**PubMed**]

Dr. Ramchandani

Well, let's jump right in and talk about anal cancer detection in the anal area, which can be challenging for providers. So, the first question I have is, why do we screen for cancer in the anal area?

Dr. Stankiewicz Karita

That is a great question. So, screening for cancer in the anal area is quite important, especially in a few groups of people who are considered at high risk for developing cancer, or high-risk populations. And let me break down the rationale a little bit. First, we don't have clinical trials that show the value of screening for anal cancer or screening for precancerous lesions. So, the rationale relies on some similarities that we have or we see in the anal canal with the cervix. First of all, the anatomy, so anatomically the anal area or canal in the cervix are very similar, particularly in areas where the cells are more susceptible to HPV infection. Second, the screening cytology for the cervix has been successful in reducing cervical cancer rates. And third, treating those precancerous lesions in the cervix show that reduce the rate of progression to invasive cancer, and we most recently have these similar data also in the anal canal. So, these similarities have led experts to believe that a similar screening method could be equally beneficial for detecting and preventing anal cancer. So, similar anatomy, same virus. Can we use the same methods and apply that for anal cancer screening? There are a few other, I will say more like indirect evidence supporting this approach. And one of them is the incidence of anal cancer is particularly high in a few groups of people or the groups that we're recommending for screening. We also have effective screening tools for detection of the anal precancerous lesions, and we can treat them before they progress to cancer.

And, I think it's also important to know that if we find and we treat or detect or prevent the cancer, even if we find an early cancer, we can reduce that morbidity and mortality significantly. And from a cost perspective, I think that screening will be more efficient because, of course, in early detection and intervention is generally more or less expensive rather than treating an advanced cancer. Finally, we have data from the ANCHOR trial. And for the audience that may not be very familiar, this was a multisite and national study here in the U.S. that actually showed strong evidence that treating these precancerous lesions can prevent a progression to invasive anal cancer. So that reinforced the importance of a screening to prevent anal cancer.

anal--penile-cancer**[04:07] Anal & Penile Cancer**

Dr. Ramchandani

As a follow-up question, what percentage of anal or penile cancers are caused by HPV? You mentioned there are certain cells that are susceptible to HPV infection, and I don't know if that relates to this question.

Dr. Stankiewicz Karita

Right. Yes, it does relate, more or less, but I will say that 90% of all cases of anal cancer are associated with what we call high-risk HPV types or high-risk HPV infections. Most of them, like 80% of them, are HPV 16, so that's the leading or what we consider the most pathogenic one. And when we're seeing patients in our clinic, I really pay attention to the HPV 16. The next one is HPV 18, probably causing like 5% of these cancers, and the rest is a pool of 10 or 12 other high-risk HPV types that are probably less pathogenic but still associated with cancer. Same with the penile cancers. I will say most of them are due to HPV 16, and then followed by the HPV 18, but we think that, in total, maybe like 50% of all these cancers are HPV-related. So, not all of the penile cancers are HPV versus anal cancer where most of the cancers are HPV-related. And, I think about the HPV infection as the necessary but insufficient for the development of these precancerous conditions or cancer. And, I tell patients it's insufficient because the infection is so common, like we all get exposed at some point in our lifetime, but the cancer itself is rare, especially in the general population. So, there are other factors that will contribute to the anal cancer progression or development. So, in that sense, I try to also reassure my patients that, yes, this is a common infection, but the cancer itself is relatively rare.

Dr. Ramchandani

So not all patients who are exposed to HPV might develop cancer, but about 50% of anal-penile cancers are related or caused by HPV, and mostly 16 and 18, correct?

Dr. Stankiewicz Karita

That's correct.

pathogenesis**[06:36] Pathogenesis**

Dr. Ramchandani

How does HPV cause anal dysplasia or precancerous lesions?

Dr. Stankiewicz Karita

That's a great question. As providers, clinicians, it's important to know so we can also explain to our patients and provide some education and counseling around that. But HPV is a virus that spreads through skin-to-skin contact. And, if you think about the area where the HPV infects in the anal canal—specifically, is the pre-anal area—in about an inch or so from the anal opening. So, it's not a lot of tissue, but the skin or that tissue is a squamous epithelium tissue, or I tell patients these thick layers of cells that is actually protecting us against infections and viruses, etc. But the HPV infects the bottom layer of that thick epithelium. They are also known as the basal stem cell layer, and these are the layers that are dividing and producing the new layers that form the skin, the epithelium. So again, if the skin is intact, we won't have the infection even if we were exposed, but the HPV can gain access to that basal layer through micro-abrasion of the skin or the mucosa, can be through intercourse, in scratching, toys, it can be anything. It can be, again, minor micro-abrasions. And once the infection is established there, the HPV is kind of like maintaining the cells. I tell the patients they take over some of the machinery of the cells and start dividing and growth and driving some cell division. And, as those cells are maturing and reaching the top of the layer of that squamous epithelium, they slough off and they release these infectious HPV virions that are ready to initiate the next round of infection.

four-screening-tools**[08:35] Four Screening Tools**

Dr. Ramchandani

So, can you describe the main test clinicians should be using to screen for cancer in the anal area? Let's say if a patient comes in and wants to be screened or should be screened, what are the main tests clinicians use?

Dr. Stankiewicz Karita

So, we have different tests. I usually tell patients or the clinicians who are listening, it's like the tests that we use for cervical cancer screening. So, we tweak it, and we make some modifications or adaptations for the anal canal, but they are essentially the same. And the screening itself is kind of like a model from the cervical cancer screening. So, we have the anal cytology, or also known as a PAP test, and some molecular diagnostic like the HPV DNA testing and the high-resolution anoscopy (HRA), which is again similar to the colposcopy exam in the cervix.

I will start with the anal PAP, which is basically we insert a swab, a polyester fiber swab that is just wet with water, with tap water, and we try to collect some cells that are on the top of that thick epithelium that are about to slough off or lose in a sense. So, we try to collect as much as those cells and we take the swab and shake that in a ThinPrep, the liquid cytology media, and we send that to the lab or the pathology lab for an evaluation. So, they will actually collect if the few cells that we try to obtain with the swab and look under the microscope, and then determine whether or not the cells are infected with HPV. With that same ThinPrep or liquid cytology sample that we use for the cytology, we send the leftover to the molecular diagnostic lab for HPV DNA detection. And, that depends on the lab and where you're practicing, but usually, what the report is the high-risk HPV types, and specifically, they will tell you if there is HPV 16 or 18, and then for the rest of them, they will just pull and report as a high-risk non-16, non-18 high-risk HPV test. So, we can do both the cytology and the HPV DNA with that single swab.

And the third tool that we use for screening is the high-resolution anoscopy. This is an exam that we can do or

we do it routinely in the office using a colposcope that will provide some light and magnification, and we use other tools like vinegar or acidic acid in a strong iodine solution, also called Lugol's solution. And, these three elements, the vinegar, the iodine, and just looking with the high magnification and light, will help me see there are any changes in the pre-anal area or the anal canal that could be associated with an HPV infection. And after you train for many, many, many exams and probably even still many years, you can get very familiar to identify those lesions by looking, again, using these tools. I usually tell patients that this exam is very subjective, so I'm usually pretty good and accurate in about 70% of the time. So, and again, as you train and see more cases, you probably will feel more and more confident. But to be a 100% sure, we actually need to obtain biopsies of these areas and send that to the lab or to the pathologist, so they can actually tell us whether or not there is an HPV infection there, if that's a low-grade or a high-grade, or a cancer, right? So, it is important to have a trained provider to do this exam, but also to have a pathologist that can actually confirm or exclude this diagnosis. So, it's a team effort really with the pathologist, with the lab, with molecular diagnostics, and again, having that clinician that can confidently see these patients and find these lesions because that is ultimately how we will prevent the anal cancer.

I also want to mention the one more tool, and if I can call it a tool, is the digital anorectal exam. Technically, I don't think about that for screening of the precancerous lesions because they are typically not palpable. So, they are flat, and if you don't use your vinegar or your light and your magnification, you won't see them. But the digital anal rectal exam, which is called DARE, can be helpful to detect an early cancer because those are usually palpable. And again, you could be detecting an early cancer that again, will have a better outcome compared to something that is more advanced and symptomatic. So, patients without symptoms can still have an abnormal DARE, and that's an important tool. Unless you don't have a finger, you don't have an excuse [not] to do it, right? So, it's an easy way. You can do it in all your patients. And again, should be easy to do it in the clinic and it just take a few minutes to make it done.

For more information, click on PMID link or attached IANS Guidelines to view Table 2: Screening Tests for Anal High-grade Squamous Intraepithelial Lesion (HSIL) and Cancer.

Dr. Ramchandani

Thank you. That was a great overview. And so, it seems like the DARE could be easily done in a lot of different clinics, while high-resolution anoscopy is really better done at a center that has the experience and the practice history of having done it before.

Dr. Stankiewicz Karita

That is true and unfortunate in a way because then we think about the access and equity for having our patients seeing these more specialized providers doing these exams. But I think at the minimum, they all should have these basic exams, and we can maybe talk a little bit in a moment about how can we make a priority of who should be referred to a clinic with high-resolution anoscopy.

Dr. Ramchandani

And that's really helpful.

screening-tips**[15:00] Screening Tips**

Dr. Ramchandani

So, from a practical standpoint, let's talk about a patient: a 34-year-old male who has sex with men, two partners in the last six months, and he's HIV negative. He has no symptoms, and he's asking for full STI screening. How would you counsel him about HPV? And would you screen him for anal dysplasia or anal cancer?

Dr. Stankiewicz Karita

That's a really relevant and very common scenario. Patients like this one are often referred to my clinic, and I usually start by providing some basic education about HPV, and especially since I think that HPV is not one of the STIs that is covered during routine STI counseling. So, I start with that. I usually try to provide some visual aids, a printed diagram or something on the screen, and try to make it simple. I explain how it affects the anatomy of the anal canal, the areas where the HPV will infect. I explain how the transmission happened, the type of lesions that it can cause, and the difference between the low-risk HPV types that are associated with warts and these high-risk HPV types that are the ones that can cause the precancerous lesions or the full name is a high-grade squamous intraepithelial lesion (or HSIL), and these are the two precancerous changes that can lead to cancer. So, I try to make that distinction clear for them.

And, I also explain that the HPV will only affect the anal canal and perineal area. That doesn't infect the colon, so it doesn't cause colon cancer. That's one of the questions that they will always ask and bring that is like, "Oh, my family member with colon cancer." So, HPV, to our knowledge, doesn't cause colon cancer, and a colonoscopy doesn't help with the prevention or detection of anal cancer. So, after that basic education, I try to personalize the discussion by stratifying the patient's risk. And according to the 2024 International Anal Neoplasia Society (IANS) guidelines, the incidence of anal cancer in men who have sex with men who are HIV negative will start to increase or rise at age 45. It will peak at age 60, but they recommend starting the screening at age 45.

So, in this case, this patient is 34, HIV negative, and doesn't have any symptoms. I will explain that, yes, their sexual behavior will put him at a high risk compared to the general population, but based on the current guidelines, we don't have to start screening until age 45. And I will explain that we're not ignoring anything, we're just following evidence-based guidance, and we will resume that screening when the person turns 45. But also making some comments that if they, of course, have anal symptoms at any point, they should be checked sooner. And, in general, I always try to tell patients is that they should not ignore anal symptoms: pain, bleeding, any bumps or lumps. They should be checked, and I rather tell them to be a false alarm than something that can be very serious, like a cancer, for example.

screen-everyone**[18:28] Screen Everyone?**

Dr. Ramchandani

So that leads me to my next question. Who do we recommend anal cancer screening for? And why these particular populations? Should we screen everyone?

Dr. Stankiewicz Karita

We should not screen everyone because anal cancer is relatively rare, but there are certain groups in the populations that are at higher risk based on epidemiological data showing higher risk of anal cancer in these populations. And these are people living with HIV, I will say those are the patients with the highest risk. Also, patients who are immunosuppressed for other reasons. For example, solid organ transplant recipients and patients who are receiving immunosuppressive therapies. There are patients without immunosuppression or who are immunocompetent, but that also are at this high risk of developing cancer. For example, men who had sex with men or transgendered women without HIV infection. And, the other group that I want to mention is women who have an HPV-related disease or cancer in the cervix or in the vulvar area. They are also at risk of cancer because we think that there could be a concomitant infection in the anal area, or the HPV easily travel or spread to the anal canal. So, they are also part of the group of people that needs to be screened for anal cancer.

For more information, click on PMID link or attached IANS Guidelines to view Table 1: Populations for Screening.

anal-area-swab**[20:00] Anal Area Swab**

Dr. Ramchandani

I think one thing that comes up among clinicians is doing molecular testing for HPV in the anal area. So, for example, swabbing the anal area for high-risk HPV types and sending it for PCR [polymerase chain reaction]. Do you do this in your clinic? And how do you counsel patients?

Dr. Stankiewicz Karita

In my clinic, yes, we use that because it just gives me an extra layer of information, particularly if we can tell whether or not there is an HPV 16 infection or one of the non-16, non-18 HPV detection. But I usually tell patients up front that I won't be surprised if it's positive. So, I give them the heads up. It will likely be positive, especially if I think about those in the group of people where HPV in the anal canal is very prevalent. For example, men who have sex with men, with or without HIV. So, I tell them it's like, "I will collect the swab, I will send it for HPV DNA testing. It will likely be positive." It won't change my clinical management that much, but again will be just another layer of information.

Dr. Ramchandani

What about sexual health clinics in general? Wouldn't that be an easier way to screen for predisposition to anal cancer or precancerous lesions? Should all sexual health clinicians just swab the anal area for high-risk HPV types in their patients?

Dr. Stankiewicz Karita

Yes, the HPV DNA can be used as a tool in the sexual health clinics or the clinics in the community, particularly if they don't have access or immediate access to a high-resolution anoscopy, which is the gold standard of care. So, the provider can do the swab, can test for the HPV DNA, and if that HPV DNA is detected or abnormal so they can follow the screening guidelines. And particularly if there is an HPV 16 infection, those are the patients that will likely or should be referred for high-resolution anoscopy because they will be at highest risk of anal cancer.

But again, paying attention to the age and the risk groups or risk stratification, we shouldn't be doing the swab in all of our patients. And sometimes I have like very young patients that they want to know, and I usually counsel that, again, it's very likely that they will have a prevalent HPV infection, but because of their young age, the risk of anal cancer will be exceedingly low, and we shouldn't do that swab in that context. But if those who are reading the guidelines, and if that's the test that we have for screening or to help us decide who will need a high-resolution anoscopy, we could obtain that in the office.

Dr. Ramchandani

So, it seems like, according to the guidelines, it could be a useful source of information to help potentially guide management, but counseling of the patient would be an important part of that clinical decision-making, so that patients know what a positive test result might mean.

hra-referrals**[23:00] HRA Referrals**

Dr. Ramchandani

You mentioned high-resolution anoscopy, also known as HRA. When would you refer a patient for HRA? And should HRA be done on everyone?

Dr. Stankiewicz Karita

Patients with an abnormal cytology or PAP test or a high-risk HPV detection should be referred for a high-resolution anoscopy. So we can do a more detailed evaluation and potentially take biopsies if we see any lesions. But one of the limiting factors is the viability or access of HRA screening. And actually, the guidelines, the IANS has developed management recommendations for both high and low HRA capacity areas. And what they mean with sufficient capacity is that your patient can have an HRA after we collected or we found abnormal screening within six months, so that's the waiting time for these high or low access to HRA. So, in the low HRA capacity areas, their recommendations really help you find or identify for the patients that need the high-resolution anoscopy evaluation more immediately.

And, specifically, these are the patients who have HPV 16 detection or those who have a PAP smear with a HSIL or ASC-H. For the audience, these are cells found during the PAP smear that are consistent with the precancerous changes, so those are the patients that, again, should be seen or evaluated with high-resolution anoscopy immediately. For the rest, there is a buffer between 12 to 24 months where we can repeat the swab and repeat the evaluation again with the cytology or the HPV DNA testing or both, if you have available in your clinic, but it gives you a little bit more of time to retest. And again, the evaluation is not as urgent as those with HPV 16 or HSIL on cytology.

Dr. Ramchandani

What about if a clinic has access really to only DARE (or digital anal rectal exams)? Let's say they have access to HRA, when would they refer a patient for HRA?

Dr. Stankiewicz Karita

If you have access to HRA, I will still follow the guidelines, right? You start with your swab cytology and/or the HPV DNA testing. If any of those are abnormal, you can send them for a referral for HRA. And then when you do your rectal exam or the digital rectal exam, if that is abnormal, you don't care about the HPV or the cytology results, you just send them for an evaluation, or if they have symptoms. So, I think symptoms will trump all of these guidelines. Again, these are just kind of like population-based guidelines, but you also, as a clinician, have to really think about your patient, right? And if they're having symptoms or if you're worried about any particular findings on exam, you should refer them regardless of their HPV DNA testing or cytology test.

For more information, click on PMID link or attached IANS Guidelines to view Table 3: Management of Screening Test Results.

worrisome-symptoms**[26:11] Worrisome Symptoms**

Dr. Ramchandani

And what types of symptoms would a patient present with that you'd be worried about that they should be referred for HRA?

Dr. Stankiewicz Karita

Things that I worry about are, for example, anal bleeding that is persistent. Like, I tell patients that having hemorrhoids, which are usually the most common cause of anal bleeding, it is fairly common, right? And it's fine. We can have anal bleeding here and there, but nothing should be persistent. So chronic bleeding from the anal canal, patients that feel bumps or lumps that are not going away or are painful, like even when they are sitting and they feel that something is bothering them, and it can be a subtle pain when they are sitting, for example. So, anal pain should also be another red flag for clinicians to obtain a more direct evaluation with a high-resolution anoscopy. So, to summarize, chronic anal bleeding, pain, bumps or lumps are most of the common symptoms that I will worry about.

And just to add another interesting layer, like the HPV infection itself is not really symptomatic. Again, HPV is a virus that will not cause symptoms. Like if you think about HSV [herpes simplex virus], for example, where patients will usually tell you that they have an outbreak, unless we really look for HPV, patients will not have symptoms. And when they develop symptoms, it's actually quite late. It's a lot of the time they already have an established cancer or there is a concerning lesion when we look under high-resolution anoscopy.

other-risk-factors**[27:43] Other Risk Factors**

Dr. Ramchandani

And so, in counseling patients, what are some of the other risk factors for anal dysplasia or anal cancer that you talk to them about?

Dr. Stankiewicz Karita

Yeah, I get asked this quite frequently, and there are several factors identified for the development of the high or the precancerous lesions and anal cancer. And, of course, the most important is having an HPV infection, which again is fairly common as we discussed. One is the sexual behavior, and most of these studies are done predominantly in patients who are men who have sex with men. And, we know that the number of sexual partners and a history of anal receptive intercourse is associated with high-risk lesions in anal cancer. Now, in persons with cervix, also having a history of receptive anal sex will increase the risk of having anal HPV or anal cancer. But, as I mentioned earlier, that having a history of HPV lesions or infection in the cervix, on the vulvar, or in other anatomical site will actually also increase their risk of having anal HPV or HPV lesions. And, I want to point out this is something important, can be a very sensitive point, particularly in women who report that they never have receptive anal sex. And this is actually a good number percentage of patients that come to my clinic and tell me it's like, "I never had receptive anal sex, or maybe I had once like 3 years ago," and they are confused on how they ended up with an anal HPV lesion or even like an anal HPV cancer, right?

And, the truth is that HPV, again, can spread in ways that are indirectly related to sexual behavior. And this is important to mention, I think, as well when we counsel patients. So, the virus cannot spread from the cervix, and I usually tell those who have vaginal intercourse that usually the primary infection probably is in the cervix or the vaginal area and then it spread to the anal canal. And, there is actually a nice study from Australia that looked at something simple as wiping from the front to the back when we use the toilet, it may actually spread that HPV from vaginal cervical area to the anal canal. So, yes, having anal intercourse is the risk factor but, again, patients who never had anal intercourse are also at risk for anal HPV.

follow-up-tips**[30:25] Follow-up Tips**

Dr. Ramchandani

What's one of the most common questions you get about anal dysplasia and anal cancer, either from your patients or from other people who are working in the field?

Dr. Stankiewicz Karita

Aside from the ones that we've been already discussing, I think one of the common questions is around the expectations for follow-up and ongoing care. And to be honest, this is a great question, but it's always a tricky one to answer. It's a tough one because we don't have any universal agreement or guidelines regarding the follow-up. We have the IANS guidelines to tell us when to start, but then you know, I think it gets less and less when we talk about follow-up schedules and following these patients. So, I usually tell patients that I will, after their first evaluation, I will see them in about six months, since our exams are very subjective. So, I bring them in six months and then after that, I think about whether or not they have lesions, or they don't have lesion if there is HPV detection or not. But basically, I try to space those visits every six, 12, or 24 months.

But, I'm also honest and tell them that I rarely discharge patients from our clinic, especially if they have some HPV DNA detection, because I think about HPV as a chronic viral infection, and this is similar to herpes or shingles, right? And I use these viruses as an example because I feel people are more familiar with them. So, there are these long stretches where the virus can be under control by our immune system, and they will not be detectable with our HPV swab or even when we do the high-resolution anoscopy. So, there won't be anything visible. But later, over time, they can reactivate and cause new lesions. And again, those lesions can potentially progress to cancer. And even in patients who are being treated, I tell them that our treatments are not a 100% effective, and we don't have an anti-HPV antiviral, like we have with herpes, HIV. And even if we treat them, there are probably some viral particles that we don't get rid of, that we left behind. Those are viral particles that can reactivate and again cause lesions down the line. So, this is why the long-term monitoring is so important in these patients.

Dr. Ramchandani

Thank you, Helen. That was so helpful, and I learned a lot from you. It was an incredible discussion about cancer and HPV-related disease in the anal area.

Dr. Stankiewicz Karita

Thank you so much for the invitation.

credits**[33:15] Credits**

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