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Welcome to Yale Cancer Answers with doctors Anees Chagpar, Susan Higgins and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week Dr. Steven Gore welcomes Dr. Sangini Sheth. Dr. Sheth is Assistant Professor of Obstetrics-Gynecology and Reproductive Sciences at Yale School of Medicine. Dr. Gore is Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore Cervical cancer, I thought that was kind of a done deal in the United States? Pap smears have not gotten rid of cervical cancer?

Sheth We have definitely made a huge impact on the rates of cervical cancer since the Pap smear really started to be used regularly for screening for cervical cancer in the 1950s. But there are still some areas where we can improve. First of all, the virus, HPV, human papillomavirus, that causes most cervical cancer is also responsible for causing several other cancers, and some of those other cancers, we do not have a way to screen for. In addition, while we have done a great job lowering the rate of cervical cancer in countries like the United States, in the developing world where they are not able to utilize the Pap smear and screen tests as well, cervical cancer still remains a leading killer among women.

Gore I sit on our research review boards here and I was surprised to see some clinical trials here at Yale involving advanced cervical cancer, and again I was just surprised to find that our community in New Haven would have people who are at risk or apparently have advanced cervical cancer.

Sheth About half of women who are diagnosed with cervical cancer in the United States are found to not have had screening tests in the last 5 years. So, while the Pap smear is available, we still have work to do in getting everyone screened whenever they are due to be screened, and there is also economic and racial disparity that exists in United States where black and Hispanic women are much more likely to be diagnosed with cervical cancer and their mortality rates are also higher.

Gore Do you think the problem is mainly one of education, is there cultural resistance to screening or is it an access problem with these patients, these non-patients, do not have access to routine gynecological care?

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Sheth I think it is a combination. I think access is certainly an issue in rural parts of the country where it may be harder to get to a physician that could perform this kind of Pap smear and exam might be more challenging. I think that there are historical and cultural barriers sometimes to getting into the

doctor's office. If you do not feel welcome and I think education is a part of it too, as an OB/GYN, I often have women who confuse having an exam with having a Pap smear, and it is not the case that every time a woman has a pelvic exam that a Pap smear is being done, and sometimes there is a lack of awareness of exactly what tests were done and so they may be under the impression that a Pap smear was done but that may not have been the case.

Gore Wow! I guess it is behooves the patient if they are having a pelvic exam for an ad-hoc reason or even a planned routine exam to ask their doctor if a Pap smear was done right?

Sheth Yeah. I would say that we probably need both parties to be a little more self-aware about the importance of communication, the patient to be their self-advocate and make sure they understand everything being done and for the provider whether it is a physician or a midwife to clearly communicate what they are planning to do and at the end of the visit what was done.

Gore And what is the sensitivity of the Pap smear? I mean if a woman is getting screened, I am not sure what the recommendation is currently, perhaps you can fill us in how often a healthy woman with no history should be getting screened with Pap smear, I know that has changed over the years, but if they are getting their routine screening, can they be pretty certain that a negative Pap means they are in good shape?

Sheth Yeah, that is a great question. I will answer the screening schedule first. Screening should not start with a Pap smear until the age of 21 regardless of any other past history and then between the ages of 21 to 29 assuming that the tests are normal, it is every 3 years with the Pap smear. What is more recent, so in the last about 15 years, is we have added an HPV test. So, as I mentioned earlier, human papillomavirus is the virus that causes most cervical cancers. And now, we have ways to test for that virus. And so, the combination of testing for that virus in addition to the Pap smear which is looking at the cells from the cervix under a microscope, that combination is incredibly powerful, and so we do that testing for women 30 and older. And the reason that we start at 30 is because of our understanding of HPV. So, HPV is a sexually transmitted virus, but it is incredibly common. So, about 80% of people who are sexually active will have HPV at some point in their life. And most of the time our bodies are able to clear and fight off the virus. And so, it is a very small percentage of people in whom the virus stays around and it is the persistence of the virus that really increases the risk of developing a precancer or maybe even a cancer of the cervix.

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Gore Now wait a minute, is the HPV virus the same one which causes genital warts? You are telling me that 80% of the sexually active population has warts?

Sheth HPV has many different strains, there are many different types of HPV,

and there are two in particular that are low risk strains, and they are called low risk because they do not have the potential to become cancer. And those two low-risk strains are responsible for about 90% of genital warts. And so, again, like I said, most people's immune system is able to fight off the virus and so that is why most people do not see genital warts or even precancer or cancer because their bodies fight it off.

Gore I see. And the ones that cause cancers, are not the same ones which are causing warts for the most part?

Sheth Exactly. Those are what we call high-risk strains and there are about 14 high-risk strains out there that are primarily responsible for causing cervical cancer.

Gore How do you screen for the virus? Is this a blood test or is this a test during the pelvic exam?

Sheth It is a test that is performed on the same sample that the Pap smear is done on. So, it does not require anything additional from the patient during the exam, it is done behind the scenes in the laboratory.

Gore On the microscope slide then?

Sheth Right.

Gore Interesting, so, 80%, why then wait until 30 to start doing the screening when so many women nowadays are sexually active at a much earlier age?

Sheth Because the HPV virus is so common and it is most common in younger people, especially in that under 25-age category and because so much of it clears on its own, we do not want to pick up infections that the body is going to be able to take care of on its own because having abnormal testing, either HPV testing or an abnormal Pap, leads to a whole series of other procedures and exams and there is downside to unnecessarily picking up infections that the body is going to be able to take care of on its own. It can cause anxiety. These exams and procedures can be uncomfortable, maybe even painful for some people and so we really want to try to narrow down to really only to have the women that are at truly increased risk to need these additional procedures. And that is why the HPV testing routinely starts at age 30.

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Gore I see. So, let us walk through this a little bit. Let us say that we have got a 40-year-old married mom, just to make it very middle America, conventional, and she is monogamous at this point in her life with her partner, her husband, and she goes in for her routine gyn exam and has a Pap smear that shows HPV infection, is that what it would show or persistence? What happens next?

Sheth It depends on the results of the Pap smear. In some cases, it may just be that instead of waiting a few years to get the next Pap smear, we do one again

a year later. If the degree of abnormality of the cells is more concerning, then the next step would be an exam called a colposcopy and that is an exam that is done in the gynecologist's office most of the time.

Gore It sounds scary.

Sheth Yeah it is a big word, but it is really just looking at the cervix with a specialized microscope. So not that different in many ways from what that woman has already been through for the exam.

Gore So, on an exam table with stirrups and so on?

Sheth Exactly. And then, the part that could be different is that if with the microscope we see any areas that are concerning or that we feel like we need more information on, then there is a small biopsy that is performed at that time and as someone who does this procedure all the time, I would say that most women tolerate it incredibly well, they often do not even know when the biopsy has been done. It can be sometimes a touch uncomfortable, but certainly the office is a perfectly appropriate space for that.

Gore Kind of like a pinch really?

Sheth Yeah, exactly.

Gore Okay, and then what happens?

Sheth Then the biopsy goes to pathology and they take a closer look at it and we get more information back as to whether there is an abnormality there and what the extent of that abnormality is. And now we are getting into what we call cervical dysplasia, often thought that as a precancer of the cervix.

Gore Funny cells that are behaving normally?

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Sheth Exactly, and there is a gradation here. So, it could be that the biopsy comes back completely benign or normal cells, which is great news for the patient. And then we would just want to still keep a close eye on them and have them come back for a Pap smear in a year. It could be that it comes back as what we call CIN-I, cervical intraepithelial neoplasia – I. The risk of that developing into a cervical cancer over the years to come is exceedingly low, and so even in that case, we would just keep a close eye with another Pap smear in a year, and the abnormalities that we really want to kind of focus in are the CIN-II and the III which are associated over a series of years with an increased risk of cervical cancer, and in that case, we factor in the patient's prior history, their age, obviously have a conversation with them about what they would be interested in pursuing in terms of treatment and we also sort of factor in their future fertility and make a plan together about what the next kind of course of action would be. But oftentimes, there is additional treatment that comes into play at that point.

Gore I am sure our listeners want to know all about that, but right now, we are going to take a short break for a medical minute. Please stay tuned to learn more information about cervical cancer and the HPV virus with Dr. Sangini Sheth.

Medical Minute Support for Yale Cancer Answers is provided by AstraZeneca, working to change the cancer paradigm through personalized medicine. Learn more at astrazeneca-us.com. It is estimated that 200,000 men in the US will be diagnosed with prostate cancer this year with almost 300,000 new cases in Connecticut alone. One in six American men will develop prostate cancer in the course of his lifetime. Major advances in the detection and treatment of prostate cancer have dramatically decreased the number of men who die from the disease. Screening for prostate cancer can be performed quickly and easily in a physician's office using 2 simple tests, a physical exam and a blood test. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital to test innovative new treatments for prostate cancer. The Artemis machine is a new technology being used at Smilow Cancer Hospital that enables targeted biopsies to be performed as opposed to removing multiple cores from the prostate for examination that may not be necessary. More information is available at YaleCancerCenter.org. You are listening to WNPR, Connecticut's public media source for news and ideas.

Gore Welcome back to Yale Cancer Answers. I am Dr. Steven Gore, and I am joined tonight by my guest, Dr. Sangini Sheth. We have been discussing cervical cancer and the human papillomavirus so far. Sangini, before the break you were walking us through

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the scenario of otherwise healthy, middle-aged women having a Pap smear and then this colposcopy test to look closer at an abnormality and maybe having one of these early premalignant or I guess low-grade malignant whatever you want to call this CIN IIs and IIIs that are of concern, and you are going to have a conversation with that patient what the options are. Can we follow through on what happens next?

Sheth Yeah absolutely. So, for most CIN II and III, there is often treatment involved and that treatment can be pursued in a few different ways. So, the goal of any treatment is going to be removing that abnormal area of the cervix. That can happen through a minor surgical procedure, often termed a cold knife conization, which typically happens in the operating room as a same day surgery or as something called a LEEP, a loop electrosurgical excision procedure. Many offices are able to do LEEP procedures in the office, and occasionally, they are also done in the operating room, again as a same day procedure. There are additional treatment options available such as cryotherapy, which is essentially freezing off the abnormal cells or pursuing that excision therapy by using laser

technology instead. So, we kind of divide treatment up into ablation or just kind of destroying those abnormal cells versus excision, which is removing the cells. The benefit of excision is that we are able to send the tissue to pathology to get even more information about what is going on. There is a small group of women, younger women, who maybe want to pursue childbearing in the future, especially if they have CIN-II, that kind of middle ground where there may be a role for observation, so keeping a very close eye with frequent exams, maybe every 6 months or so because there is about a 25-30% chance that a CIN-II type of lesion could regress on its own, and I have now mentioned this plan for future childbearing a few times and the reason that that plays a role is that there is some evidence that removing or destroying cells on the cervix can lead to a small but slightly increased risk for future pregnancy. And so, we want to be very careful in what sort of treatment plan we pursue in that group of women. The types of risks we talk about are preterm labor or premature rupture of membranes and sometimes scarring of the cervix, so anytime we talk about surgery, there is a risk of scarring in the area of the surgery.

Gore So the problem is not getting pregnant, it is the question of maintaining a normal pregnancy to term?

Sheth Typically yes.

Gore Interesting. So, once the area has been removed, is the patient then free of the HPV?

Sheth The kind of treatment rate or regression rate with these types of treatments is very good, and what we typically do is follow them with a Pap smear every year for the first

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two years and assuming that those come back normal, after the two years immediately following treatment, they can return to kind of routine screening, the same as before all of this happened.

Gore I see. And do you think the HPV is gone from their body or is it still latent somewhere?

Sheth HPV is tricky and it is hard to know partly because it is so common and sometimes it is hard to differentiate what is continued infection versus a reinfection, and to kind of separate that out is not always clear.

Gore Do we know how the virus causes cancer?

Sheth The virus is able to embed itself into our normal cell DNA and it kind of takes over those cells and starts to replicate out of control, the way everything kind of other cancer cells work.

Gore I see. Interesting, but that does not happen right away apparently if the virus is prevalent.

Sheth Exactly, so the natural history from HPV infection to invasive cervical cancer is very long, which is actually what makes it so that we can have these screening test because we are able to catch abnormalities early and intervene, and that is what is responsible for driving down the rates of cervical cancer that we talked about at the very beginning.

Gore So, how effective is the HPV vaccine, and who should be getting it?

Sheth In addition to screening for cervical cancer since 2006, we have had this amazing opportunity to prevent both HPV infections and its downstream consequences including cervical cancer with HPV vaccines. The HPV vaccine is routinely recommended for 11- to 12-year-old boys and girls, but it can be given as early as age 9, and the key is that it is given prior to any exposure to HPV, which is why it is at a young age. The vaccine is known to be very safe, very effective, the most recent vaccine to come onto the market in 2014 is protective against 9 types of HPV, within that 9 types is the two that cause 90% of genital warts and also about 85-90% of cervical cancer. So, there is a lot of protection to be gained from the vaccine and when started early, when started before the age of 15, it is just 2 doses of 6 to 12 months apart. If the series is started at 15 years or older, then it is a 3-dose series and it is FDA approved and recommended to give through the age of 26. So, if someone gets a late start, it is perfectly okay and we are able to vaccinate them until their 27th birthday.

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Gore For some vaccinations like hepatitis B for example, it is recommended that people have subsequent blood tests to see if they in fact reacted with immunity to the vaccine. Is there anything like that with these HPV vaccines or you just get your series of shots and hope for the best.

Sheth At this point, there is no other recommended screening or testing, it is just getting the 2 or 3-dose series and so far there is, whatever data has come to date has shown really good results in countries like Australia, they are having incredibly high vaccination rates. They have in just a few years seen a dramatic decline in their genital warts at a population level. Unfortunately, in the United States, our rates of vaccination are lagging and there is a lot of opportunity there to get our rates to be much higher.

Gore Do we know what the factors are there?

Sheth Yeah. That is a great question and there is a lot of research that has come out since the vaccine first came out in 2006 to show that HPV vaccine is not at all associated with early age of sexual activity or increase in number of partners and really the message needs to be that this is about cancer prevention. There is not a lot of other cancers that we can prevent with just a simple shot, and so the other reasons that we have come to know that are associated with lower rates of vaccination, a lot of it come sits with the providers, it is really incumbent on them to recommend the vaccine, recommend it with their full

endorsement.

Gore This would be pediatricians right? I mean because the girls are not seeing gynecologists at age 9.

Sheth Exactly. So, family physicians, pediatricians, and to stress again, this is about cancer prevention and it does not have to be about sex or sexually transmitted infections.

Gore Is the vaccine covered by insurance and by Medicaid?

Sheth Absolutely. The vaccine is covered based on the CDC's recommendations, so between the ages of 9 and 26, in girls and young women, Medicaid covers it, private insurances cover it, and for people who are uninsured or under-insured, there is a whole federal program, the Vaccines for Children program that covers all vaccines for children under 18 including the HPV vaccine.

Gore That's fantastic, I did not know about that. And so, boys do not have a cervix, and so are we just vaccinating them so they do not get warts?

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Sheth There are few reasons to vaccinate them. Boys can spread HPV to their female partners and so there is benefit in vaccinating our boys and our girls for that reason; certainly to protect them against genital warts; and I should mention there are three types of HPV vaccines out on the market, only two of them Gardasil and Gardasil 9 are able to protect against genital warts and those are the two that are recommended for boys. And there are a few other reasons. So, as I mentioned, HPV is associated with several other cancers in addition to cervical cancer, that includes head and neck cancers and also anal cancer, and so those have the potential of being protective for boys and men as well.

Gore And is that dependent upon the kind of sexual activity that the individual participates in?

Sheth Exactly.

Gore So, head and neck cancer from somebody who is having oral sex with an HPV infected partner and anal cancer from somebody who is having either oral-anal contact or genital-anal contact in a sexual encounter?

Sheth Exactly.

Gore I see. And of course we do not know what our boys are going to be up to when they are becoming young men and certainly we do not want them getting cancer and oral sex is pretty prevalent in our mainstream population now.

Sheth Right, exactly. And that is why this is not about trying to predict who is going to be doing what type of sexual activity at what age, it is really that there is an opportunity to prevent multiple types of cancers and we should do everything we can to protect our communities.

Gore I can imagine that it must be challenging for some parents who are dealing with their 9-year-old little third or fourth grader and this is forcing them to confront the fact that this young child is soon to be adolescent and a young adult and will be sexually active, and I can imagine that is kind of challenging to confront for some parents.

Sheth I can definitely understand as a parent myself, it is a very sensitive topic to be thinking about, but as a gynecologist, I will also say that for a patient to have to go through multiple exams and all the procedures that I discussed earlier that come with having to diagnose and treat precancer and we did not even get into what is involved if someone has cancer, I would say that to replace all that with 2-3 shots is far worth it.

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Dr. Sangini Sheth is Assistant Professor of Obstetrics-Gynecology and Reproductive Sciences at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer. You are on WNPR, Connecticut's public media source for news and ideas.