Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale, New Haven. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert on Myelodysplastic Syndromes. Yale Cancer Center Answers features weekly conversations about the research diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. Tonight you will hear a conversation about cervical cancer and HPV with Dr. Sangini Sheth. Dr. Sheth is Assistant Professor of Obstetrics, Gynecology and Reproductive Sciences at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar Sangini, let's start by talking about HPV. What exactly is it?

Sheth It stands for human papilloma virus. It is a sexually transmitted infection that is very common, particularly among young people, and it is associated with a range of diseases from precancerous conditions to genital warts to cancers in a variety of different areas of the body.

Chagpar If this is sexually transmitted, is this something where people can just wear condoms or protect themselves in that way to prevent transmission or is this something that can be transmitted regardless?

Sheth Condoms are absolutely important as a way to reduce HPV infection but it is not 100% because the virus lives on the body and the condom only covers a certain area of the body and so while it is going to help, people still have to be concerned about HPV infection particularly because it is so common in the general population.

Chagpar So if you want to reduce the risk of transmission, how can you do that aside from condoms and safe sex?

Sheth One of the most effective way that we have currently is by using the HPV vaccine. The most recent vaccine that became available actually covers 9 different strains of the virus, 7 of which are associated with different types of cancers and 2 of which are associated with almost all genital warts, and so that is an excellent form of prevention for a large amount of the diseases that HPV infection causes.

Chagpar Who can get vaccinated? Can everybody get vaccinated or are there certain guidelines for who gets vaccinated and who cannot?

Sheth There are guidelines for who should get vaccinated. The vaccine is recommended for routine use among 11-12 year old boys and girls and they can be vaccinated as early as the age of 9 and if they are not vaccinated at 9 or at the core age of 11-12, then the window opens up and we are able to offer women and men the vaccine up until age 26.

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Chagpar Here is the problem that I have had with a lot of our discussions on this show about HPV vaccine. I think we understand that the HPV vaccine is important because it is able to prevent transmission of this virus which could be cancer causing, but the vaccine really only came about in the last few years and so if you have a population of people who are in their 30s, their 40s, their 50s, what do they do, they cannot be vaccinated, do they just kind of say, okay, we are going to take our chances, or what can they do to reduce their risk?

Sheth So for women 27 and older, the key for them is really going to be screening, cervical cancer screening to reduce their risk as much as possible for going on to develop cancer. The goal of screening is to catch a lesion before it becomes cancer and to try to deal with that before it gets to something more concerning.

Chagpar What is that screening and how often should that happen?

Sheth Screening is in the form of a combination of Pap smears and also more recently, we have been using HPV testing which is basically a test that looks for the presence of the DNA of the HPV virus.

Chagpar But I thought that HPV is on all parts of your body, so will you not find this DNA anyways?

Sheth The test is actually looking for a set of high risk strains firstly, so that is about 14 different HPV types that are most commonly associated with cervical cancer and then some of the other cancers that HPV is known to cause, and because HPV, as you just commented, is so common, we do not start doing that HPV testing routinely until women are 30 years or older in order to avoid having younger people who are often able to clear the virus on their own from testing positive and needing to go through unnecessary tests.

Chagpar So some people, especially when they are younger, can clear the virus and it will not go on to cause cancers.

Sheth Absolutely, young, healthy women are very commonly able to clear HPV infection on their own, so it is important that we allow their body that time to do that so that again we are not doing unnecessary procedures on all these women.

Chagpar So this HPV DNA test, how exactly does that work, is that a blood test or is that a smear, how exactly does that work?

Sheth It typically can be performed on the same sample that the Pap smear is performed and so it does not really require anything additional from the patient. It is one exam and at the time of the exam, we collect the Pap smear specimen and it is actually done within the laboratory level, the different types of tests on that one sample.

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Chagpar Say I am 30 or 40 but I am otherwise really healthy, how do you know that I would not be able to clear that HPV on my own even if I tested positive?

Sheth If someone was 30 or 40 years old and they tested positive, if their Pap smear showed normal cells, we would actually just retest a year later and give the body the time to potentially clear. If the Pap smear showed abnormal cells and there was HPV vaccine present, then we would say the next thing to do is to actually look a little bit more closely at the cervix with a procedure called colposcopy where we look with a microscope and take small biopsies, just to give the pathologist more information.

Chagpar We will talk more about how we can detect cervical cancer early, but let us suppose somebody tested positive for the HPV DNA and their Pap smear was completely normal and they felt normal and they were otherwise healthy, waited a year, repeated the Pap smear and the HPV DNA test, and let us suppose the same thing happened, they remained colonized with HPV, they were not able to clear it, is there a way to treat HPV?

Sheth There is no way to treat HPV. At that point we would be concerned about a persistence of HPV and when it comes to risk of cervical cancer, it is really the persistence of HPV infection that is most concerning because as I said HPV is very common, it can be cleared and so at the point in which it becomes persistent, that is when the risk increases and so in the situation that you just described, the second time around we would go ahead and want to perform a colposcopy because there is no other real treatment for the virus.

Chagpar At that point you do a closer look and essentially you are really looking at the cervix to see whether there are any abnormal areas and if there are abnormal areas, you would biopsy them, but if you do not see any abnormal areas, then what happens?

Sheth That is a really interesting question. There have been some studies recently that have actually shown there may be some benefit to still doing random biopsies and that sometimes we can pick up on random biopsies some very small abnormalities that we cannot see even under a microscope, so there would potentially be a role for still doing the random biopsies and otherwise, we would follow women very closely and have them come back again in 12 months for another Pap smear and HPV test and what works to our advantage you could say, is that HPV infection has a very long natural history from time of infection to when it causes cervical cancer and so even though 12 months or 1 year may sound like a long time, it is actually not at all a very long time in the broad-spectrum of the disease.

Chagpar So the HPV DNA test is really to stratify the patients in terms of their risk because it is not something that you can say, oh you have got HPV DNA, I can clear that and voila we have eliminated your

risk or drastically reduced your risk of cervical cancer. It is more so that if you see this you can advise somebody that they are at risk and need to be followed more closely. Is that right?10:49 into mp3 file https://az777946.vo.msecnd.net/cancer/2015%200913%20YCC%20Answers%20-%20Dr%20Sheth_232473_5.mp3

Sheth Absolutely.

Chagpar So when we talk about following more closely, you mentioned getting Pap smears once a year, what are the general recommendations for how often women should get a Pap smear, should they not get them once a year or is it longer than that?

Sheth The answer to that question has changed quite a bit in the last 10 years and so it can get pretty confusing. The current recommendations from several professional societies including the American Cancer Society is that most women do not need to be screened every year anymore, which has been the recommendation previously, so most women as long as their screening stays normal can go every 3-5 years. For younger women, women under 30, the recommendation is every 3 years and for women over 30 as long as the Pap smear and their HPV test are both negative, they can actually go every 5 years.

Chagpar Let's go back to the situation where you have now done this colposcopy and whether you have seen abnormal areas or done random biopsies where there are no abnormal areas, if you take these biopsies and you see abnormal cells, tell us a little bit more about the stratification of what you can see under the microscope and what impact that has for the patient.?

Sheth At the time of colposcopy, there are a variety of different kind of things that we look for under the microscope, so we actually apply a solution to the cervix made up of acetic acid so it is a mild vinegar like solution and that solution helps any abnormal areas stand out. Those abnormal areas may turn white and so those white areas may be areas that we consider biopsying. We may see some very fine abnormal vessels and so that will be another indication for an area we would want to biopsy and finally, we are looking for an area of the cervix that has a variety of different names, but it is a junction where the outer part of the cervix meets the inner lining of the cervix and we really need to be able to see that zone because that is the zone where often abnormal cells first start to develop and if we did not see that zone, then we would consider it not a complete colposcopy and then we would certainly want to also get a sample, what I often call a scraping, of the inner canal of the cervix, so those are some of the descriptive terms that we are looking for under the microscope and any of those things would probably prompt us to do a biopsy.

Chagpar We are going to learn more about what you look for in the biopsy, what cancers could come about and precancers and how we treat those after we take a break for a medical minute. Please stay tuned to learn more information about cervical cancer and HPV with my guest, Dr. Sangini Sheth.

Medical Minute There are over 13 million cancer survivors in the United States and over 100,000 here in Connecticut. Completing treatment is an exciting milestone but cancer and its treatment can be a life changing experience. Following treatment cancer survivors can face several long-term side effects of cancer including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources for cancer survivors are available at federally designated Minute

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comprehensive cancer centers to help keep cancer survivors focused on healthy living. The Survivorship Clinic at Yale Cancer Center focuses on providing guidance and direction to empower survivors to maximize their health, quality of life and longevity. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale- New Haven. More information is available at yalecancercenter.org. You are listening to WNPR, Connecticut's Public Media Source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Sangini Sheth. We are talking about cervical cancer and the role of HPV. Right before the break, Sangini, we were talking about HPV, we were talking a little bit about screening for cervical cancer, one other thing that continues to come up is that HPV is sexually transmitted and for the most part, it is the leading cause of cervical cancer, is that right?

Sheth That is right.

Chagpar Are there any other causes of cervical cancer, I mean smoking, drinking, obesity, all of the other things that we think about, genetics?

Sheth There are things that increase the risk of cervical cancer such as smoking which is an important risk factor and there may be a genetic component. Some of that we do not fully understand and there is a very small percentage of cervical cancer that is not associated with HPV infection, and so that area is still under study that we do not fully understand.

Chagpar One of the questions some people may wonder about, is if you have never been sexually active, do you still need a Pap smear?

Sheth At this point, I would say yes because of that small percentage that is not associated with HPV infection, until we have more understanding of that.

Chagpar Let's pick up where we left the story before the medical minute which was you go and you have a Pap smear as we all should every 3-5 years which is the new recommendation and if they find abnormal areas, especially with a colposcopy, they will do a biopsy. Now on that biopsy, many of us get results that may not be something that the audience would completely understand. We frequently are told things like there are some funny looking cells or precancer

or a little bit of precancer or true cancer, can you explain what all of this is, it sounds like there is a spectrum of change and all of it means different things to the patient, is that right?

Sheth That is exactly right. There is a spectrum and so how I would describe it to patients is there are normal cells of the cervix and then there are low-grade abnormalities often that may show up in report as something called CIN-1 cervical intraepithelial neoplasia and those cells, while they look abnormal, the risk of that developing into cervical cancer is very, very low and so the treatment done for something like that would actually just be observation and repeating the Pap smear again

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in 12 months because even something like that can clear on its own over time. The next grade that we see is what I would describe as a moderate dysplasia or CIN-2. The risk of that developing into cervical cancer is a little bit higher and so then depending on a variety of factors, the age of the patient, how long that CIN-2 has been there, what their future childbearing plans or fertility plans may be, we may have a discussion about again keeping a close eye on that by repeat Pap smear or colposcopy or we may have a discussion about doing something that is a little bit more aggressive and I will get into that but the last two areas of the spectrum are something called CIN-3 which is high-grade cervical dysplasia. It is often in the same category as noninvasive cervical cancer, which is something that we all take very seriously and most of us would treat in a surgical way and then there is actual invasive cervical cancer at the other end of the spectrum. So the more aggressive ways to treat the moderate and high-grade dysplasias are through definitive treatment with surgical excisions and what that means is actually some providers are able to do these procedures in the office and sometimes it requires going to the operating room and it means just taking out a small portion of the cervix, basically trying to get rid of all those abnormal cells before they spread or before they get more abnormal. For the CIN-3 and certainly for the invasive cervical cancer, at that point, we are talking about something along the lines of hysterectomy and again for invasive cancer at that point the patient will be referred to an oncologist and they would need to have staging performed and then the treatment gets pretty complicated based on the stage they are at, so absolutely there is a spectrum.

Chagpar Let's pick up on a few of those nuances, you talked about the most aggressive way of treating CIN-2, moderate dysplasia, is taking a little bit of the cervix, how does that affect a patient's fertility and their ability to have children and so on and so forth?

Sheth The potential risks involved with doing that procedure when it comes to future pregnancies is that you may have either shortened or weakened the cervix so it could increase the risk of miscarriage or preterm labor and on the other end you could have caused scarring of that cervix making it harder for

that patient to dilate and have a normal pregnancy and labor course. In general, the thought is that the risks are increased although the literature shows varying degrees of risk but for now, it is an important factor to take into consideration for young women.

Chagpar And then for the CIN-3 and the invasive cancers, it is a more aggressive surgical approach with a hysterectomy, do the patients have to have their ovaries taken out at the same time?

Sheth It is a great question. With CIN-3 for many of those women just taking out a portion of the cervix is a very reasonable approach. We may take a little bit more of the cervix out just to be safe, so it is not an absolute that those women have to have a hysterectomy, certainly by the time they have invasive cancer it is a different story, and there it just depends on the stage whether they will be surgically treated or treated with radiation or chemotherapy, but in general, for those women for whom hysterectomy is recommended, in the setting of cancer, it is probably recommend that their ovaries are taken out. When hysterectomy is performed for other indications, the conversation is different.

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Chagpar You mentioned staging a few times now, talk to us a little bit about staging of cervical cancer. Many of us on the show have talked about staging and our audience may be aware that staging is a way of getting to understand how bad or how aggressive a course of a cancer that will be based on a number of factors, but those factors vary based on different kinds of cancer. Tell us a little bit about what is involved in terms of staging for cervical cancer and how you do that?

Sheth Cervical cancer staging is interesting. It is a little bit different from the other gynecologic cancers, in that it is a clinical staging and part of the reason is because cervical cancer is incredibly common in the developing world, much more so than here and so the rest of the world does not have the same access to the technology in terms of CAT scan or MRIs or even some of the more advanced surgeries that we may do here, so by clinical staging, the exam, we are looking at what does the cervix look like? What does the tissue around the cervix feel like? Is the cancer just within the cervix, does it feel like it has spread to the tissues around the cervix? And then the additional studies that are supported for this staging are looking inside the bladder, looking inside the rectum to see if there is obvious disease there and so again this is kind of how clinical staging is done. Then the lower stage disease is the less advanced cancer that can be treated surgically with a hysterectomy, it is usually described as a radical hysterectomy meaning a little bit more of the tissue around the uterus and cervix is taken out and then for more advanced stage cervical cancer, it has not been shown that a hysterectomy or surgery is of any benefit because the disease has spread to such a degree and in those cases, the patients are really treated with chemo and radiation.

Chagpar Tell us a little bit about the epidemiology of cervical cancer that we see here in the States, one would hope that with the ubiquity of cervical cancer education and the availability of screening with Pap smears that the majority of cervical cancers that we see are early stage, is that true?

Sheth About half of the cervical cancer diagnosed in the US is early stage cervical cancer and another 30 or 35% is stage II to III leaving about 10% that is more advanced stage cervical cancer and really the issue as you just said is about screening. The women who have not been screened in the last 5 years or greater than that are at the highest risk for developing cervical cancer and having a high stage.

Chagpar In stage II and III is surgery still an option, or are they only treated with chemotherapy and radiation?

Sheth Even within the stage II and III, they are broken down into sub categories and in the very beginning of stage II, there would potentially still be a role, but certainly when you get further down into II and by the time you get to III, there is usually not a role for surgery.

Chagpar Interesting, because when we compare across cancers, I would have hoped that for cervical cancer it would be much more like breast cancer where the vast majority of patients present with stage I 27:15 into mp3 file https://az777946.vo.msecnd.net/cancer/2015%200913%20YCC%20Answers%20-%20Dr%20Sheth_232473_5.mp3

disease and an even larger proportion of patients could have surgical management for definitive curative intent, but it sounds like that for cervical cancer, it is not as quite as good.

Sheth It is not, I will say that cervical cancer is not as common as breast cancer, there is probably about 12 to 13,000 cases diagnosed each year of invasive cervical cancer, and then the percentages as I mentioned before, where about half of that is early stage.

Chagpar Tell us a little bit more about chemotherapy and radiation therapy. Many times on this show we have talked about the fact that chemotherapy is really more systemic, it goes all over your body, it kills cancer cells all over your body, radiation is really more localized, how do you, in terms of cervical cancer, decide whether you are going to use chemotherapy alone or radiation therapy alone or do you use both altogether in later stage cancers?

Sheth I am not a GYN oncologist, so I do not tend to treat the women once they have been diagnosed with the invasive cancer. My understanding in general though is that when radiation is applied, it usually has a boosting affect with chemotherapy and so it is a combination, but the combination is really to support the radiation.

Chagpar So the key really seems to be that people need to be aware that cervical cancer exists and they need to be aware that HPV is a leading cause that they

should get vaccinated and make sure that they get screened so that they can find these cervical cancers early.

Sheth Absolutely, I cannot stress enough the importance of prevention with the vaccination and the vaccination has almost no risk and is safe and is incredibly effective and then the second arm of prevention being screening.

Dr. Sangini Sheth is Assistant Professor of Obstetrics, Gynecology and Reproductive Sciences at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.