

Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This week Dr. Wilson welcomes Drs. Daniel DiMaio and Divya Patel for a conversation about papillomaviruses. Dr. DiMaio is Waldemar Von Zedtwitz Professor of Genetics and Professor of Molecular Biophysics and Biochemistry and of Therapeutic Radiology. He is also a Scientific Director and Deputy Director of Yale Cancer Center. Dr. Patel is Assistant Professor of Obstetrics, Gynecology, and Reproductive Sciences.

Wilson Let us start off by having you both describe what papillomaviruses are?

DiMaio Viruses are a small microorganism, but papillomaviruses are among the smallest known. They infect the sources of our bodies such as the skin, the mucous membranes of the oral cavity, and the genital tract and most infections do not cause any disease at all, you do not even realize you are infected. But some infections cause warts, so the warts that you might have on your hands or feet are caused by papillomaviruses, and they can also cause genital warts, where the viruses can cause cancer, but this is a rare outcome and one that typically takes many years or even decades to occur.

Wilson Let's start off by each of you telling us a little bit about your background and how you became interested in this subject matter.

Patel I am an epidemiologist by training and most of my research currently is focused on cervical cancer prevention and early detection, and I got into this field in a bit of a roundabout way. My training was in infectious disease epidemiology, and I became very interested in some of the longer term consequences of infection. It was a time when there was a lot that was being a newly understood about HPV, the human papillomavirus, and it was also very interesting because clinical practice was evolving at the same time so we were starting to use HPV screening as part of cervical cancer early detection and it was at the same point when the clinical trials for the new HPV vaccine were coming out. So really it was just a very exciting time to become involved, and it was a great time as a younger investigator to become integrated into this field of HPV. It was a good fit with some of my research interests in women's health and clinical research.

Wilson That is terrific, and Dan, how did you get interested in this topic?

DiMaio I am primarily a laboratory basic researcher, and when I was an undergraduate at Yale I became interested in viruses, I was fascinated by how they can take over a cell and grow and then later I became interested in how they can cause a cell to proliferate out of control and cause cancer. So

3:07 into mp3 file http://yalecancercenter.org/podcasts/2011_1204_YCC_Answers_-Drs_DiMaio_and_Patel.mp3 when I began, we actually did not know there were any human tumor viruses, we suspected it, but it was not known, and over the past 20 or 30 years we realized that about 15% of all cancers in people are caused by viruses, and so this is an important area and one that we can attack by vaccination and other public health measures.

Wilson Tell us a little about what is different about papillomavirus compared to any other kind of virus, and give us some more specific information about how they relate to cancer?

DiMaio These are viruses that infect lots and lots of people and this is a very prevalent infection and there are billions of people worldwide infected by these viruses. What is interesting, is that they can cause cells to proliferate out of control and cells are particularly the type called epithelial cells, which as I said line the body, and their most important medical outcome is cancer, particularly of the uterine cervix, and cancer of the cervix accounts for about 250,000 deaths per year worldwide, but also other anogenital sites and more recently we have understood also some head and cancers, about 20% of all head and neck cancers are also caused by exactly the same viruses that cause cervical cancer. So it is a problem both in men and women.

Wilson Are all cervical cancers related to this virus or only some of them?

Patel The best evidence that we have suggests that practically all, I would say 99.5% of cervix cancers are caused by HPV. Some of the other cancers that Dr. DiMaio was mentioning, some of them are just as likely to be associated with HPV and some of them are less commonly associated with HPV, but cervix cancer is just about 100% HIV associated.

Wilson Are there different types of papillomaviruses?

Patel Right now we know of over 150 different types of HPVs. There are about 40 of those that infect the anogenital region, and even within that there are certain types that are considered high risk or oncogenic for cervical cancer. So there are about 15 that have been identified as high risk for cervix cancer.

Wilson How do you tell the difference between these different types of papillomavirus? Do we understand yet what it is about certain types that put patients at higher risk for cancer?

DiMaio They are defined based on DNA sequence analysis.

Wilson And tell me what that is Dan?

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DiMaio That is when as you look at the genes of the virus, which encode the various functions of the virus, and they are composed of a molecule called DNA which has specific subunits that are in a particular order and by looking at the order of the subunits you can distinguish one virus type from another, and what's interesting about these viruses are that different types cause certain disease. So one type might cause disease warts say on you feet, but not cause warts on your hand, one might cause warts on your hands, but would not cause warts in the genital region, and by the DNA sequence seen and by other molecular tests that we can now use, we can distinguish these various types.

Wilson Do we understand yet, if we know a particular sequence, why that sequence might put someone at higher risk for certain kinds of cancer compared to a different sequence? Can we figure that out yet?

DiMaio To a certain extent. It's not completely understood but the viruses have genes called oncogenes, which are genes that actually cause the cancer and the oncogenes of some type are slightly different from types of oncogenes from other types. So by looking at their particular molecular characteristics we can predict to a certain extent which one's would be higher risk or not.

Wilson We touched on it a little bit, but could you go into a little bit more detail about some of the risk factors for developing HPV?

Patel Sure, I just wanted to reiterate something that Dr. DiMaio had mentioned, that HPV is so common. In fact, it is the most common sexually transmitted infection in the US and worldwide. So in terms of risk factors, they estimate that almost 80% of anyone who has been sexually active will have HPV at some point in their life. Basically, the most well established risk factors are having many sex partners, so a high number of lifetime sex partners, starting sexual intercourse at early ages, and also just simply being young. Younger people in general, people under 25, are at highest risk of acquiring new HPV infections.

DiMaio This is actually an amusing story, the first hint that cervical cancer might have a sexually transmitted cause, were studies carried out in Italy in the 1840s where physicians realized that all the nuns in the religious convents, none of them got cervical cancer because they were not sexually active and it was the women in town that were getting the cancer. That was the first hint that sexual activity may be correlated with the risk of this cancer.

Wilson I see. Talk to us about screening. What is screening? What types of screening activities are available in the United States?

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Patel It is interesting, for HPV, it is not something that we generally test for. HPV infections are detected only when there is some sort of clinical disease such as genital warts that Dr. DiMaio had mentioned, or cervical, anal, vaginal, or other precancers or cancers. So, HPV testing is really just one part of cervical cancer screening at this point, and during screening you would test for HPV in the same way that you do a regular Pap smear, which is what we do for cervical cancer screening. It is way that we take cells from the cervix and look to see whether there are changes in the cells that have been caused by the HPV infection.

Wilson And you can tell that by what sort of changes? Is that under a microscope?

DiMaio This is primarily done under a microscope; the cells are stained for certain chemical constituents and by looking at the shape of the cells, how large they are, how they pick up different stains, the cytologist can say, this

looks like a precancerous lesion, and in fact, the Pap smear test, which Divya mentioned, really needs to be recognized as one of the most successful public health interventions we have ever invented. And this is not high-tech but it has reduced the incidence of cervical cancer in this country by probably 80%. In the 1930s, cervical cancer was a leading cause of cancer death in women in the US, and now it is actually relatively rare because of the success of the Pap smear.

Wilson I see.

DiMaio And we hope to be able to add HPV testing on top of the Pap smear to get better risk estimates and better control of this disease.

Wilson Let us take a scenario where someone undergoes screening and they test positive for HPV. What sort of intervention might we recommended at that time for them, or what sort of clinical course should they follow?

Patel As we just discussed, HPV is known to be the primary risk factor for cervix cancer, and that really indicates to the clinician that there is probably closer follow-up that needs to happen. I can talk a little bit about what is routinely done in clinical practice and I think this is really interesting because the guidelines have changed pretty recently and so a lot of people may not be aware of some of the new screening guidelines and how that relates to HPV testing. Now the major organization in the OB/GYN field, which is the American College of Obstetricians and Gynecologists, recommends that screening for cervical cancer not occur before age 21. It used to be that they would recommend screening within about three years of the first sexual intercourse, so young woman were getting screened. They have reviewed those guidelines and have shifted the

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recommendations to start no earlier than 21. So for women that are 21 to 29, basically they get cervical cancer screening, Pap smears, about every other year and that also is a shift from what we used to think of as an annual screening. So that was the big change for women 30 and up. There are a couple of different of options, one would be the screening every other year using the Pap smear and the second option, as Dan was mentioning, was adding the HVP test on top of the Pap smear, so using it as a co-test. So, the big change means that if women are negative on both the Pap smear and HPV test, they do not need to

come back for screening any earlier than three years. So the next screen would happen in three years from the first test.

Wilson Were these guidelines changed in terms of the frequency and moving the age because the data were evaluated and just doing it earlier seemed to not really make a difference?

Patel Absolutely. The data were reevaluated and as we are learning more and more about the natural history and the disease process of HPV and cervix cancer, we have to step back and review the guidelines and clinical practice. The big concern was that we know that treating very young woman could have some negative consequences, or negative impacts, especially with respect to future childbearing. So the concern was that if you screen females early and then if you find that they are positive, and actually treat them, you could be increasing the risk of some negative outcomes down the line. So they really stepped back and shifted the guidelines for the starting age because of those reasons.

Wilson So you mentioned that after 30 we are going to add the HPV testing onto the Pap smear, and you said if someone was negative, then they would not have another checkup perhaps for three years, but what if that testing reveals that someone is positive? How does that change the course?

Patel There are very specific guidelines in place also for further treatment and management of women. What I mentioned before was the routine screening. That is the every other year, or if you are negative, every three years. But if a women is determined to be positive for HPV then that shifts the guidelines and she may need to come in more frequently, maybe every six months or twelve months for repeat screening, and that is again usually done through a combination of both the Pap test and then visualizing or examining the cervix more closely under a scope.

Wilson I see, and this is something that's done as an outpatient in the gynecologist's office?

Patel Yes.

Wilson Okay.

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DiMaio Another reason to keep in mind as to why they feel comfortable with the current age guidelines is that it takes a long time for the cancer to develop, and so we are fortunate in that regard because we have time to do these testings and find these lesions and also many of them do get better on their own. So if you were to test every time you found the lesion, you would probably be over-treating because the vast majorities do get better on their own.

Wilson I see, commonly like warts in children on the finger, for example?

DiMaio Right, they might come and go.

Wilson I see.

DiMaio But if someone has a persistent infection or a Pap smear looks particularly worrisome because of the cellular abnormalities, then it is important to be more aggressive about continuing the monitoring and actually treating people.

Wilson We are going to take a short break for medical minute. Please stay tuned to learn more information about papillomaviruses with Drs. DiMaio and Patel.

Medical

Minute The American cancer society estimates that the lifetime risk of developing colorectal cancer is about 1 in 20 and that risk is slightly lower in women than in man. Early detection is the key, when detected early, colorectal cancer is easily treated and highly curable. Men and women over the age of 50 should have regular colonoscopies to screen for this disease. Each day more patients are surviving the disease due to increased access to advanced therapies and specialized care. New treatment options and surgical techniques are giving colorectal cancer survivors more help than they ever had before. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale to test innovative new treatments for colorectal cancer. New options include a Chinese herbal medicine being used in combination with chemotherapy to reduce side effects of treatment and help cancer drugs work more effectively. This has been a medical minute and more information is

available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and I am joined by my guests, Drs. Dan DiMaio and Divya Patel and we are discussing papillomaviruses. In the first half of the show we covered a lot of ground in terms of what screening is for the virus, some of the

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changes in clinical follow-up that might take place, but let us shift gears a bit and talk about what we can do to actually try to prevent this from happening and I understand that relatively recently there has been the development of a vaccine?

DiMaio Yes, this is regarded in the medical community as a terrific breakthrough. This is the ability to prevent a cancer by vaccination, which is something we have wanted to do for many decades and this is a reality now, thanks to the HPV vaccine. The virus is composed of really only one major protein, the virus particle itself, and it turns out that if you express this protein in cells it will spontaneously form virus particles, a single viral protein, and this virus particle can trick the immune system to raising the defenses against the real infection. So, we can vaccinate with these virus particles, they non-infectious, they cannot cause disease, they do not have any DNA or genes in them, but they can elicit a very potent immune response that would prevent future infection and that is the basis for this vaccine.

Wilson And, that is how it really works? It stimulates ones own immune system to get fired up and recognize this invader should it become present down the line?

DiMaio Yes, that is right. It is the type of molecules made by immune system called antibodies that actually bind to the real virus and prevent it from infecting cells, and it is extremely effective in clinical trials, among the most effective vaccines that were developed and more than 95% of people who are vaccinated are protected.

Wilson And it is that something that is lifelong? Will it prevent the infections for the next 50 years or we do not know?

DiMaio We do not know. The vaccine has been out there for 5 or 6 years and so far the protection is durable, but it is conceivable that the protection will wane with time and people may need booster shots, but that is not the case yet.

Wilson What do you think it has only been available for 5 or 6 years? Why was it not something we sorted out 20 years ago? Obviously the problem has been around for 100 of years, a lot longer than that.

DiMaio Yes, the real breakthrough was in 1983 when the German physician scientist named Harald zur Hausen made the seminal discovery that the HPV is present in essentially all cervical cancers and that was the finding for which he won the Nobel Prize and basically that was the first real clear clue that it was actually a human papillomavirus. Then, it took the next several years for laboratory people to figure out what the virus particle actually was and figure out how to make the vaccine, produce it on large scale, and do all the clinical testing. This is actually quite rapid from

19:00 into mp3 file http://yalecancercenter.org/podcasts/2011_1204_YCC_Answers_-_Drs_DiMaio_and_Patel.mp3 the time the virus is first identified as a cause of cervical cancer until the time the vaccine is used, less than 30 years, and that is actually quite rapid.

Wilson I see. And the big question in my mind is who should get this vaccine?

Patel Again that is the great question and keeps changing and evolving. This vaccine has now been in clinical use since 2006. So, it was approved in 2006 by the Food and Drug Administration and within a month of that approval the CDC, or the Centers for Disease Control and Prevention, recommended routine vaccination of females, ages 11 and 12 and then catch up vaccination up to the age of 26.

Wilson What do you mean by that, the catch up vaccination?

Patel Meaning that eventually it should be incorporated into the regular pediatric vaccines scheduled, but until then we need to make sure that

girls up to the age of 26 are getting the vaccine and so that is considered catch up vaccination.

Wilson Okay.

Patel That has been out for about five years now for girls. For boys, the situation has been very different. In 2009, I believe, there was a recommendation for what they call permissive use in boys, meaning that the decision to vaccinate is really left up to the healthcare provider and the patient and the patient's family. So it is a very different type of recommendation than a routine recommendation for girls and that has a lot of implications for people's feelings about the vaccine for boys versus girls. It also has a lot of implications for insurance coverage for vaccines, so in the United States, when the CDC issues that type of recommendation, most of the major insurance providers pick up the vaccine and cover the cost. So that is a big factor in access to the vaccine. An exciting breakthrough that just happened about a month ago was that the CDC went back, or the advisory committee to the CDC's vaccination strategies, reviewed the data for males and they really looked at it carefully in terms of efficacy data that have come in the last few years and they issued a routine recommendation for boys ages 11 and 12. So that came out just at the end of October and now the CDC is reviewing that for approval.

DiMaio I think an important point that we should discuss with the audience is I wonder why vaccinate kids that are so young? The vaccine really works best if it is given before a subject has ever encountered the virus for the first time. So the only reason for vaccinating at the young age is to catch kids before they become sexually active. If you wait, if you delay vaccination for whatever

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Wilson I see, but once someone has been exposed to HPV, then it may be completely ineffective?

DiMaio I would not say that it is ineffective because it turns out the vaccine protects against several different types of HPV. The vaccine that is most commonly used in this country protects against four types and someone

might not be exposed to all four types at once, and so I think even if someone has become sexually active there is value to vaccinating but clearly your best shot of preventing the infection is to vaccinate early.

Wilson Is there just one type of vaccine, one company that makes the vaccine or other options?

Patel There are a couple of options as I have mentioned and the most commonly used vaccine in this country is a vaccine called Gardasil. That protect against four types, 2 of them HPV 16 and 18, in particular, are the ones that are basically related to about 75% of all cervical cancers, and then in addition, it also covers HPV 6 and 11, which are the types that are responsible for almost 100% of genital warts. So that one is called Gardasil and that is manufactured by Merck. There is another vaccine called Cervarix which is manufactured by GlaxoSmithKline and that vaccine only covers the cervical cancer causing HPV types, so HPV 16 and 18.

Wilson It is interesting to me how they have slightly different coverage, where the companies developing these vaccines, obviously independently from one another, and just strategically made a scientific, perhaps corporate decision, to take their product in that direction. Why they are so different?

DiMaio Yeah, I think they made some internal calculation about the value of including the genital wart types or not and they reached different conclusions. They are both great vaccines against 16 and 18 and provide very high protection against those two virus types.

Wilson Are you aware of the companies adding additional types or are we pretty much set where we are?

DiMaio No, there are additional vaccines in clinical trials now that have additional types. I think it is up to 8 types or 9 types that are being tested. But as Divya mentioned, there are 100s of papillomavirus types, they are probably 40 high-risk types so we are never going to get all of the types in the vaccine and the vaccines are specific, in that if you are vaccinated against type 16 and 18, you do not get much protection against other high risk types. So that is one of the limitations to the vaccine that they do not cover all the types and an important implication of that, is that even if someone is vaccinated, they are not fully protected because they are not protected against the

24:50 into mp3 file http://yalecancercenter.org/podcasts/2011_1204_YCC_Answers_-_Drs_DiMaio_and_Patel.mp3 types that are not in the vaccine. So a woman that is vaccinated or a girl that is vaccinated still has

to get Pap smear testing because otherwise they are just as exposed as they were before vaccination to type 31 or type 45 and so for, so they have to maintain Pap smear testing.

Wilson I have read a little bit about some of the controversies with this because just in the lay press, for example, a vaccination of a child where the parents might say well that is not necessary for my child and my child is not going to be sexually active, so we do not need to do that sort of thing. I would say that is one of the controversies. The other is what sort of side effects if any are associated with the vaccination?

Patel Yes, I will take the second question first. The side effects of both vaccines, Gardasil and Cervarix, have been shown to be very safe in addition to their really high efficacy. They are the main side effects that you would see with any other injections, slight fever or pain at the site of injection, a little bit of dizziness or nausea but beyond that there really has not been anything that has been shown to be directly associated with the vaccines.

Wilson And is that what it is, a single injection or do you need a series?

Patel That's another great question. This is a vaccine that needs to be administered in three doses and so you have the first dose and then the second dose is two months after the first and then the third is six months after the first dose. Another thing to keep in mind is that this vaccine is unusually expensive. Its retail price is \$130 per dose and then there is usually an additional fee on top of that for administering the vaccine. So it can cost patients up to \$200 per dose for the vaccine so a three dose series gets very expensive. In terms of your first question, I think that is something that has been highlighted like you said in the lay media. It is interesting though most of the surveys that have asked the parents about how they feel about the vaccine, across the board over 3/4th of parents are willing to accept the vaccine for both their sons and their daughters. So I think what we are hearing in the lay media is a more vocal, but small group of parents.

Wilson Well, that is what often tends to make the news.

Patel Exactly.

DiMaio I think it is also worth emphasizing that there have been over 35 million doses of this vaccine given and there have been no documented serious side effects that can be quickly attributed to the vaccine. This vaccine is very safe although parents may be hesitant to vaccinate a 12 year old or say, my child is not going to be sexually active. Well they will be in their lifetime, because the

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protection is better when they are vaccinated early that is why it's needed now.

Wilson This sounds like an incredibly important public health discovery that is essentially non-toxic and extremely helpful. This is a major medical breakthrough.

DiMaio Yeah. I think it is fair to say that this is probably, in my mind, the most important medical breakthrough maybe in the last five years in terms of cancer prevention, if not longer. There are still 250,000 women a year dying of this disease, and they are all totally preventable if we get the vaccine cheaper out to people.

Wilson Of course.

DiMaio It is also worth mentioning that it is not just the cancers we focus on, namely cervical or some of the other anogenital cancers, but within the last several years we have learned that HPV also causes a substantial fraction of head and neck cancer and the same type that causes cervical cancer, type 16 that is in the vaccine, causes head and neck cancer, and so I think it is likely that the vaccine will protect against that as well.

Wilson It may take us a little longer to approve that since that is a slightly older population perhaps?

DiMaio Well it turns out that with the HPV associated head and neck cancer, it is not that much older. And even for the service, it is going to take awhile, we have not actually proven the vaccine prevents cancer because it takes 20 years to get the cancer. It certainly prevents the abnormalities that lead to cancer so we are confident it will prevent cervical cancer but we do not know for sure for another 10 to 15 years.

Wilson In the closing of the session, is there any particular research in the pipeline that you are currently working on in your laboratory along these lines?

DiMaio We are interested in how the viral genes actually cause cancer and how the virus actually gets inside the cells. So we are doing experiments trying to identify the cellular pathways that allow papillomaviruses and other viruses that enter cells and also a cellular pathway that lead from the viral genes to the cancer itself. What we found is that in cancer cells, even many-many years after the cancer has developed, the cancer cells still need the viral genes, and if you can turn off the viral genes, the cancer no longer can grow.

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Dr. Daniel DiMaio is Waldemar Von Zedtwitz Professor of Genetics and Professor of Molecular Biophysics and Biochemistry and of Therapeutic Radiology. He is also a Scientific Director and Deputy Director of Yale Cancer Center. Dr. Patel is Assistant Professor of Obstetrics, Gynecology and Reproductive Sciences. If you have questions I would like to add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.