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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. Gore is joined by Dr. Linda Niccolai for a conversation about the HPV vaccine and its role in reducing the risk of certain cancers. Dr. Niccolai is an Associate Professor of Epidemiology and Microbial Diseases at the Yale School of Public Health and Director of the HPV Impact Project, and Dr. Gore is Director of Hematologic Malignancies at Smilow Cancer Hospital.

Gore What is epidemiology? I think a lot of our listeners are really confused by that term. We see it in the newspapers all the time.

Niccolai Simply put, epidemiology really the study of trying to understand who gets sick, why they get sick and what we can do to prevent it.

Gore And how do we figure that out? What is the process and what kinds of things do you study?

Niccolai Epidemiology is a broad discipline, and people approach it from different angles. My approach has been really to do population-based science. We study people in communities, we study people in healthcare facilities, through interviews and conversations and looking at records and things like that, we identify patterns of disease. Epidemiology can really be focused on any disease, my interest has been in sexually transmitted infections and we try to understand why people are at risk and who gets sick. And if we have that information, then we can implement prevention programs to reduce the burden of disease in populations.

Gore The papilloma virus, that is the wart's virus right?

Niccolai HPV or human papilloma virus is actually a group of viruses. There are over 100 different types of HPV and they cause different diseases. Some papilloma viruses cause warts on the hands and the feet, like plantar warts. Some papilloma viruses cause warts in the genital area, so these are genital warts. And then there are about 15 types of HPV, the ones that many of us are really concerned about that are oncogenic, they can cause cancer. There are about 15 types of HPV that are sexually transmitted that can cause 6 different types of cancer. It is a broad, broad class of viruses.

Gore And do the HPVs that cause cancer not also cause warts?

3:08 into mp3 file https://ysmwebsites.azureedge.net/cancer/2017-YCA-0716-Podcast-Niccolai_309959_5_v1.mp3

Niccolai That's right, there are different types or subtypes. The common ones we hear about that cause genital warts for example are HPV types 6 and 11. HPV types 16 and 18 are the ones that cause about 70% of cervical cancer. And then there are numerous other types that cause a smaller portion of cervical cancer and also cancers of the anus, the vagina, the vulva and penile cancer and some head and neck cancers as well.

Gore Wow! I just learned something new because I did not know that and I was always thinking that the people who had genital warts would be worried that they were more at risk for some of these things, but I suppose that if you have gotten genital warts, which are also sexually transmitted, you might have gotten some of other HPV viruses along the way? Is that likely?

Niccolai That's right. The HPV types that cause genital warts are transmitted sexually as are the types that cause these anogenital cancers. So, again, the HPV that actually caused the genital warts is not likely to cause one of these cancers, but if you have been exposed to one type of HPV, it is possible you have been exposed to the other types that cause cancer as well.

Gore And I guess the converse should also be understood, that just because you do not have genital warts, does not mean you have not been exposed to a bad HPV and should not be getting your GYN screening Pap smears and things like that, right?

Niccolai That is exactly right. HPV, the sexually transmitted human papilloma viruses, are incredibly common, and in fact, I describe them as ubiquitous. Up to 80% of people who are sexually active will acquire an HPV infection at some point during their lifetime. So, almost everybody gets an HPV infection. The good news is that most of those infections are self-limited, the body's immune response kicks in, clears the infection, people do not have symptoms, there are no consequences. I mean people often do not even know they have ever been infected. What we worry about is the small percentage of infections that are persistent infections. And these are the ones that can go on and cause these different types of cancer. And that is exactly why screening is important and those guidelines should be adhered to.

Gore And the vaccination issues, that is something that we have to think about hopefully before people become sexually active, is that right?

Niccolai Absolutely, before people become sexually active. In the United States, the first vaccine was licensed in 2006. Since then, we have gotten 2 more vaccines, so there are currently 3 vaccines that are licensed to prevent HPV infection in the US, and we have had them now for over a decade. The routine recommendation is for all adolescents, boys and girls, to be immunized at ages 11 or 12, and the reason for that age is because the vaccines are only prophylactic in that they only prevent the acquisition of a new infection. If somebody already has an HPV infection, then the vaccine has no therapeutic effect. So, it is critical to receive the vaccine before any likelihood of exposure through sexual behavior.

6:34 into mp3 file https://ysmwebsites.azureedge.net/cancer/2017-YCA-0716-Podcast-Niccolai_309959_5_v1.mp3

Gore Is there any difference between the 3 vaccines, is there a reason why a physician would choose A, B or C?

Niccolai Currently there is only vaccine that is available in the US. We have a vaccine that prevents 2 types of HPV, type 16 and 18. We call that the bivalent. There is a quadrivalent vaccine that prevents types 16 and 18 that cause 70% of cervical cancers as well as type 6 and 11 that cause most cases of genital warts. The vaccine, really the only vaccine that is available in the US today, is a 9-valent vaccine. It provides protection against the 2 types that cause genital warts and 7 oncogenic types of HPV. It is a really great vaccine and that is the one that we should be using today.

Gore Yeah that seems like that is what I would choose if I could get 9 instead of 2.

Niccolai Absolutely.

Gore Could you explain to our listeners why this is important for boys as well as girls?

Niccolai Boys can get several types of cancer caused by HPV. They get anal cancers and penile cancers as well as some types of head and neck cancers in addition to genital warts, so those are clearly all outcomes that we would like to prevent in boys. There is a little bit of misperception out there I think that it is really a vaccine just for girls and it prevents cervical cancer and that may be due to the fact that when the vaccine was first approved in the US, it was really marketed for girls as a cervical cancer prevention tool. I think if we could do it all over again, we might have rolled out the vaccine a little bit differently because even though we have had the recommendation for boys since 2011, the first recommendation in 2006 was only for girls, and then in 2011, boys were included. So, we have been able to immunize boys now for 6 years, but those rates still lag behind the rates for girls, and I think it is this continuing misperception that it is not needed or necessary for boys but really nothing could be farther from the truth.

Gore Is there any thought, setting aside cancers for which the boys may be at risk, that by immunizing both boys and girls, there will just be less transmission of the viruses in general so that like polio or measles by immunizing the majority of people, we bring down the rate of transmission?

Niccolai Yeah, absolutely. We call that herd immunity, which is if you achieve a high enough level of coverage in segments of the people, then people who are not immunized are protected merely from the lower population prevalence, and in fact, Australia is a good example of that where they have had a girl only immunization campaign, but they have seen significant reductions in things like genital warts in boys because if you drive down the rate of infection in girls,

there would just be less transmission in the population. Unfortunately, in the United States, we

9:38 into mp3 file https://ysmwebsites.azureedge.net/cancer/2017-YCA-0716-Podcast-Niccolai_309959_5_v1.mp3

have not achieved a high enough coverage in girls for there to be that level of population protection. So, immunizing boys and girls both provides individual benefit, but if we can get the population coverage higher, then more people will be protected.

Gore And I guess we know just from a lot of the vaccination controversy that is in the press that there are many individual parents who see the whole vaccination question as risks and benefits for their child, understandably, and this idea of societal good does not necessarily come into play?

Niccolai Right, which is also unfortunate. I do think there is a disproportionate amount of concern about the HPV vaccine in terms of its safety record. The safety profile of this vaccine is robust and reassuring. We know from the clinical trials the rigorous scientific studies that were done that there are no serious adverse events that are associated with this vaccine. We now have 10 year of what we call post-licensure monitoring. So, tens of millions probably by now, even hundreds of millions of doses of this vaccine have been given and no safety signals have emerged, and there are very robust monitoring programs. So, the vaccine is a safe vaccine, it hurts like any immunization hurts, and one effect of this vaccine would be fainting.

Gore Fainting!

Niccolai Yeah, kids faint after getting this vaccine.

Gore More than other vaccines?

Niccolai No, not more than other vaccines, but it could happen after any immunization. So, the recommendation is that after receiving this shot that a child sit for 15 minutes before they get up and leave the doctor's office.

Gore It was always very frustrating to me as a parent.

Niccolai Waiting for 15 minutes?

Gore Oh my God! They had their shot, let's get out of here.

Niccolai No, let them sit for 15 minutes, just make sure they are okay and then they can go. And again, if you think about the fact that it hurts and fainting is a risk, those are things people need to know about, but when parents do a risk-benefit calculation, those are the risks; the benefit is preventing 6 types of cancer later in life.

Gore What is the Scuttlebutt on the Internet? What are people worried about?

12:27 into mp3 file https://ysmwebsites.azureedge.net/cancer/2017-YCA-0716-Podcast-Niccolai_309959_5_v1.mp3

Niccolai Unfortunately, the autism controversy lingers despite the fact that there is no evidence, no scientific evidence of any link between vaccines and autism.

Gore Any vaccine, for sure?

Niccolai Right. I think the scuttlebutt as you say is that people confuse anecdote with science. There may be an instance where a child gets a vaccine and then maybe they maybe get a headache a day later. Gore Or they got strep throat or something.

Niccolai Right, these things happen and that is what we call a background rate of strep throat and headaches and other things. So, what we have to do is really compare the rate of these outcomes to those who are not immunized. Then, when you do that, just because B happened after A, does not mean that A caused B. People confuse anecdote with all of the scientific evidence.

Gore Gotcha. This is such an important topic and I am really looking forward to delving into it more after our medical minute, but right now, we are going to take a break for that medical minute. Please stay tuned to learn more information about the HPV vaccine with my guest, Dr. Linda Niccolai.

Medical Minute Support for Yale Cancer Answers is provided by AstraZeneca, committed to providing targeted cancer medicines for patients. When it comes to cancer treatment, one size does not fit all. More information at astrazeneca-us.com. It is estimated that over 200,000 men in the US will be diagnosed with prostate cancer this year with almost 3000 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.

15:03 into mp3 file https://ysmwebsites.azureedge.net/cancer/2017-YCA-0716-Podcast-Niccolai_309959_5_v1.mp3

Gore Welcome back to Yale Cancer Answers. This is Dr. Steven Gore, and I am joined tonight by my guest, Dr. Linda Niccolai and we have been discussing the human papilloma virus and its vaccination and cancer. Linda, before the break, we were talking about barriers to vaccination, and you mentioned that some of it is just concerns, really unfounded concerns. I seem to remember when the vaccine came out, there was concern about by giving this vaccination because

we were promoting promiscuous sexual behavior.

Niccolai Yes, that concern was raised, and again we have 10 years of data, a lot of great scientists doing great work, looking at that question and there is not one single study that shows any evidence of increases in sexual behavior because kids have been immunized. That is just not happening and there is a lot of data to support that.

Gore I cannot even imagine that kids really pay much attention to what they are getting shots for. Maybe in adolescence they do a little bit.

Niccolai It depends on what age they get the vaccine. The vaccine is recommended at ages 11 and 12, and it is also recommended at that same visit that the child receive shots against meningitis, the meningococcal vaccine and the DTaP vaccine. So, if at an 11-year-old well-child visit the clinician says, okay there are 3 shots that you are due for today that will prevent meningitis, whooping cough and cancer, I am going to give you these 3 shots, do you have any questions, I think most parents would say "I don't have any questions, it sounds great." And there does not have to be a whole discussion around the fact that HPV is sexually transmitted. In fact, we do not talk about how meningitis is transmitted. We just talk about the diseases that are prevented. So, if the vaccine is presented in sort of this routine and bundled way, you are right, kids may not even know plus the vaccine if they do get into that conversation, and kids should be reminded that there are a lot of other sexually transmitted infections out there.

Gore Right, it is not going to protect against syphilis, for example.

Niccolai No, or HIV or anything like that, gonorrhea, chlamydia.

Gore Gotcha. And you participate in something called an HPV Impact study is that right?

Niccolai That is correct.

Gore What is that? What is the Impact?

Niccolai It is really, really exciting. We have been funded by the Center for Disease Control and Prevention, the CDC in Atlanta, since 2008 to monitor the impact of HPV vaccines at the population level. What we do is surveillance, state-wide surveillance, for high-grade precancerous cervical lesions.

18:09 into mp3 file https://ysmwebsites.azureedge.net/cancer/2017-YCA-0716-Podcast-Niccolai_309959_5_v1.mp3

Gore In Connecticut?

Niccolai The whole state of Connecticut. If a woman has an abnormal Pap smear, which means there is the presence of HPV, she might be followed up with a biopsy where a small sample of the cervix is sent to a pathology lab and can be diagnosed with these precancerous lesions. Cancer is a chronic disease and there is a natural history and there are different stages. What we are looking

at is before women are diagnosed with invasive cancer, we are looking at the precancerous lesions. And what we have seen is really dramatic, I think even I am surprised by what we found, that in the 10 years since we have had this vaccine, we have seen reductions in these high-grade cervical lesions of up to 60% in young women, and these are lesions that are clinically very significant. They are associated with a lot of follow-up, women had to go back for multiple exams and Pap smears and biopsies, and there is the psychological impact of having been diagnosed with a precancerous lesion. We are seeing really dramatic declines, which to us is evidence that the vaccine is impactful in doing what we thought it was going to do, which is to prevent cancer.

Gore If you have only had this funding since 2008, how do you have the baseline of the high-grade lesions from before the vaccine?

Niccolai That is a great question. We have had the vaccine since the middle of 2006 and our first data on the rate of these lesions is from 2008. We feel that what we saw in 2008 was probably even pre-vaccine impact because these lesions are ones that are typically diagnosed anywhere from 2-5 years after infection.

Gore I was going to ask you, how do we know that, are there natural history studies where they can date the onset of the infection and then follow, how does that work?

Niccolai That is very complicated and there are natural history studies, but it is very difficult to know when someone got infected in relation to the diagnosis of a high-grade lesion, very difficult to know, which again brings me back to the important point, which is immunization really needs to happen before any exposures.

Gore Fascinating, I guess there are issues about whether even 11 and 12 is young enough in our society, unfortunately?

Niccolai Right, that's true, very unfortunate. The vaccine is actually licensed. It can be given as young as age 9. So, if there were a reason to be concerned about exposures, it is FDA approved to begin at age 9. For most kids though fortunately, 11 or 12 should be good enough.

Gore How has the uptake been in Connecticut? Do you have any sense of that?

21:25 into mp3 file https://ysmwebsites.azureedge.net/cancer/2017-YCA-0716-Podcast-Niccolai_309959_5_v1.mp3

Niccolai The uptake in Connecticut has been good. We know that right now in Connecticut, about 70% of adolescent girls have received at least 1 dose. It is currently a 2-dose regimen, used to be 3 doses and that has changed to 2 doses. Now boys and girls just need the 2 doses. Adolescent girls in Connecticut, about 70% have received at least 1 dose and about 45% of boys have received at least 1 dose.

Gore Much less in boys.

Niccolai Yes, but boys are still catching up. And those numbers are higher than the national average. In Connecticut, we should applaud that, we are doing better than the national average with coverage, but when you think about 70% of girls receiving at least 1 dose, that is still 30% of girls, who by age 17 have not received any doses and over half of all boys, so I do think while we should applaud our coverage, there is more work to do, it is still not optimal, it not where it should be, it is not where it could be.

Gore What is the uptake in Australia since you had mentioned that?

Niccolai Australia is over 80% and they achieved that very quickly. Within a year or two, Australia was up at 80% coverage and they did that primarily through school-based vaccination programs. Kids in school get immunized in school. In the United States, we do not have school-based immunization programs. Our immunizations are provided almost exclusively in the clinic-based settings. So, kids need to go to their doctor, their pediatrician or their primary care provider, they need to be offered the vaccine, and they need to accept the vaccine. The way we do this in the United States, there are lots of opportunities for kids to fall through the cracks. After 10 years have not achieved the same level of coverage Australia reached within a couple of years.

Gore It is really interesting because I am old enough that I went to school and I got a sugar cube with a polio vaccine, everybody did, we all lined up, we got the sugar cube and that was somewhere in the early 1960s, right?

Niccolai Right.

Gore Why doesn't our society work that way anymore?

Niccolai I think it is complicated and there are a lot of different ways to answer that question. I think one thing I can say is that vaccines, they are one of the greatest public health successes of this century, and in some way they are victims of their own success because they have done such a great job of reducing the burden of so many diseases, that I think people today do not remember polio, they do not remember diphtheria, they do not remember these diseases, so I

24:28 into mp3 file https://ysmwebsites.azureedge.net/cancer/2017-YCA-0716-Podcast-Niccolai_309959_5_v1.mp3

think for some people it just does not seem as important anymore because we have lost the salience of the severe outcomes that can happen when people do not get immunized.

Gore There was a big public will to get everybody to get rid of polio because it was such a devastating disease. That's interesting. And I suppose that the whole body politics if you will in terms of societal acquiescence and individual choices is probably a different discussion than it was.

Niccolai Right, and that is one of the challenges that we face. Another challenge we face is because we rely so much on this clinic-based approach to providing

immunization. It really speaks to the important role that healthcare providers have. It is mostly pediatricians.

Gore They have to remember to do it.

Niccolai They have to remember to do it, and they have to think that it is important, and I am often reminded that pediatricians and other clinicians who provide care to children and adolescents that they are people too and they come with their own thoughts to the clinic encounter, to the medical encounter with their own perhaps priorities. I have had clinicians in Connecticut say to me, "oh! I don't offer it to my boy patients because there is no benefit." And that is simply not true. There is some lack of knowledge there and I think another challenge that pediatricians face is that the outcome that we are preventing with these vaccines are cancers that are mostly diagnosed in adults. Pediatricians are not treating patients with cervical cancer, so it is an outcome that may be less salient to them in the context of providing care to an 11-year-old, whereas they think much more seriously perhaps about meningitis and whooping cough because those are diseases that they do see. I think the fact that these cancers happen 10, 20, 30 years down the road, for some clinicians, they think about it as not urgent, and it is something that can wait. And the problem with waiting is that kids may not come back to that doctor or kids might be exposed. To me the real key in increasing coverage with this vaccine is to work with the clinicians to make sure that they have the knowledge they need and the awareness they need to really recommend this vaccine with a lot more urgency and consistency.

Gore Let us say a kid has not been vaccinated, either a boy or a girl, and starts his or her adult healthcare journey, and I think probably most likely this would be in a girl who starts seeing a gynecologist because she becomes sexually active or just feels like this is the thing to start doing, and let us say the doctor determines that she has not been vaccinated, is there a role for vaccinating young adults?

Niccolai Yes, there is, and I am actually very glad you brought that up. The routine recommendation is for ages 11 and 12, but there is a recommendation for catch-up vaccination. So, girls who have not been immunized at 11 or 12, can be immunized up to age 26, and boys can be immunized up to age 21 and some boys, for example those who are immunocompromised,

27:52 into mp3 file https://ysmwebsites.azureedge.net/cancer/2017-YCA-0716-Podcast-Niccolai_309959_5_v1.mp3

can be immunized up to age 26. So, there is a role for catch-up vaccination, but I think we are relying on that a little too much, there are not too many other vaccines that I can think of that we do not offer on the recommended schedule. The catch-up is for kids for whatever reasons who fell through the cracks at 11 and 12, but we should be relying on that as our primary immunization strategy.

Gore Do you find that there are particular strata or communities that are less likely to be served? I can argue it either way, I might think that public health

clinics that sponsor kids that are less economically advantaged might in some ways be better at this than the kind of frou-frou suburban private doctors, that is just my guess.

Nicolai Well, your guess is a good one and that is exactly right. We do see higher rates of coverage with this vaccine. That is offering by pediatricians and acceptance among parents in populations that have a higher poverty rate and that are more racially and ethnically diverse. So, higher proportions of black patients, Hispanic patients and patients living in poverty, they actually have better coverage. Gore Fascinating, isn't it? I mean that is kind of backwards of everything else.

Nicolai Yeah, we call it a reverse disparity. And in contrast, so more in the suburbs, as you say, those rates tend to be lower and I think it is more parents thinking that they know what is best for their child and doctors more reluctant to push it, resulting in that population actually having lower coverage.

Dr. Linda Nicolai is an Associate Professor of Epidemiology and Microbial Diseases at the Yale School of Public Health and Director of the HPV Impact project. 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.