

# Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio



## *Hosts*

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## Viruses and Cancer

### Guest Experts:

#### **Dan DiMaio, MD, PhD**

*Waldemar Von Zedtwitz Professor of  
Genetics; Professor of Molecular  
Biophysics and Biochemistry and of  
Therapeutic Radiology; Deputy Director,  
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#### **Linda Niccolai, PhD**

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Microbial Diseases; Director of HPV-  
IMPACT Project*

## **Yale Cancer Center Answers**

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*Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is [canceranswers@yale.edu](mailto:canceranswers@yale.edu) and the phone number is 1-888-234-4YCC. This week, Dr. Chagpar welcomes Dr. Dan DiMaio and Dr. Linda Niccolai. Dr. DiMaio is Waldemar Von Zedtwitz Professor of Genetics and Professor of Molecular Biophysics and Biochemistry and of Therapeutic Radiology. He is also scientific director and Deputy Director of Yale Cancer Center. Dr. Niccolai is Associate Professor of Epidemiology and Microbial Diseases and Director of the HPV-IMPACT project in the emerging infections program. Here is Anees Chagpar.*

Chagpar Let's start off by having you tell us a little bit about what both of you do to start the conversation about cancer and vaccines and viruses.

Niccolai I am an epidemiologist and I have been doing public health research for about 10 years now here in Connecticut, most of my time at Yale. My work is really focused on infectious diseases and in particular, infections that are sexually transmitted. I was very excited in 2007 when a new vaccine for the human papillomavirus, which is a very common sexually transmitted infection, became licensed and available in the US. This was a very exciting time because we now have a vaccine that is very effective at preventing an infection that we know causes several different types of cancer. So the potential for prevention is really tremendous and for about the past five years or so, I have been focusing my work on how best to achieve that potential.

Chagpar Dan, tell us a little bit about what you do particularly as a virologist and also as Deputy Director of Yale Cancer Center. When most people think about cancer, they think about genomics, they think about genetic abnormalities, we do not often think about cancer being associated with viruses.

DiMaio I have been studying viruses and cancer for about 30 years and became very excited with the prospect that we could understand cancers, because viruses are simple and in animals we have know for well over 100 years that viruses can cause cancer, but in the last 30 years or so we really came to understand that viruses cause cancer in people, and now we recognize that about 15% of all cancers in the world are caused by viruses, and what is exciting is that we have approaches to handle viruses, to prevent infection, by vaccination and other public health measures. That is 15% of all cancers we could eliminate by using these sorts of strategies. This has been a very exciting time.

Chagpar The idea that cancer is potentially preventable and that we can vaccinate people against cancer is really exciting, is this just for a particular type of cancer, or is it a very broad spectrum of cancers? What kinds of cancers are we talking about, and what kinds of viruses cause these kinds of cancer?

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- DiMaio Some of the cancers are quite common, the hepatitis virus for example, there are several types of the hepatitis virus that cause liver cancer, about 80% of all liver cancer is caused by a virus infection ultimately. Cervical cancer, or cancer of the uterine cervix, 100% are caused by the human papillomavirus infection, but there are a number of other types of cancers, some lymphomas, some forms of Hodgkin disease, some types of nasopharyngeal cancer, and some head and neck cancers that are also caused by viruses. So it is a very specific set of viruses and a specific set of cancers.
- Chagpar Linda, you talked of human papillomavirus as a sexually transmitted disease and I think that many of us understand viruses and sexually transmitted diseases. So, are these viruses the ones that cause cervical cancer, or do they also cause other kinds of cancer? Can we really vaccinate and prevent these cancers?
- Niccolai There are actually lots of different types of HPV. There are over 150 different types of the virus and these different viruses cause different types of disease, for example, some types of HPV cause warts on the hands and feet and other types of these viruses cause warts in the genital area and other types cause infections of upper reproductive tracts, so like this cervix, and those are the infections that can go on to produce cervical cancer. The cervical HPV infections are very common, millions of people have these infections at some point in time in the US, but it is important to realize that most of these infections do not go on and develop into cervical cancer. There is good screening with the Pap smear test that can detect early precancerous lesions. So even though these infections are common, they do not often go on and produce cervical cancer if women receive proper screening.
- Chagpar So women should get screened with Pap smear to see if they have early signs of precancerous lesions, but I find the whole concept of viruses causing cancer and having vaccines that may actually prevent cancer, really exciting and novel, so tell us a little bit about how that works? Should everybody get vaccinated, and when should they be vaccinated? Is this something that you have to get vaccinated multiple times for?
- Niccolai Currently there are two vaccines that prevent infection with HPV. There is Gardasil which protects against four strains of the virus. It protects against type 6 and 11 that cause 90% of genital warts and type 16 and 18 that cause 70% of cervical cancers. The bivalent vaccine is called Cervarix and it protects against infections with type 16 and 18. The guidelines are very clear that the routine recommendation for vaccinations is that boys and girls at ages 11 and 12 get the vaccine and it is a 3-dose series to be given over six months, and it is ideal to give the vaccine to very young adolescents because the vaccine can prevent infections with HPV, but cannot treat it, so it really needs to be given before people become sexually active. We also have catch-up

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recommendations, so if for some reason an adolescent does not get the vaccine at age 11 or 12 they can get the vaccine up to age 26 and they can still receive protection that way.

- DiMaio I think it is also worth pointing out that within the last 10 years or so, we have appreciated that the same viruses also cause a substantial fraction of head and neck cancers. Cancer of the tonsils, cancer of the base of the tongue and the vaccine which is developed to prevent cervical cancer we believe will also prevent head and neck cancers as well.
- Niccolai That is an interesting point, because when the vaccine first came out in 2006 it was only approved and licensed for use in women, and that recommendation has changed since 2011, the recommendation is for boys also to receive routine recommendation. I think part of that was because the vaccine also prevents some anal cancers, but head and neck cancers as well. So the boys are currently lagging behind the girls in terms of coverage, but it is really important to get the message out that the vaccine does prevent more than just cervical cancer, as a way of making sure more boys get vaccinated.
- Chagpar Let's talk a little bit about how we get that message out. Is this something that is being taught in schools? Is this something that our family physician should be talking to our youth about? How do we get that message out, because it sounds like it is a blanket recommendation?
- Niccolai It is, and pediatricians are typically the ones who would give this vaccine to their patients and they are very well aware of the vaccine and I am sure they are doing their best to promote its usage. A couple of barriers have been that it is a relatively new vaccine and some people tend to be wary of that. And the other thing is that it is a vaccine that protects against a sexually transmitted infection. So many parents think that their children do not need it. I will tell you one thing that is not a barrier is that the vaccine is covered by all major health insurance companies and it is also covered by federal programs for uninsured or underinsured teens. So anybody who wants the vaccine should be able to get it without the issue of cost. Currently the latest estimates from some national survey data are that only about 50% of adolescent females have gotten at least one dose of the vaccine and only about a third have received all three doses. So, clearly the uptake rates are suboptimal and we need to do a lot more work around promoting the vaccine and really understanding what the barriers are. I think those are still empirical questions at this point.
- Chagpar Can you only get this virus through sexually transmitted routes?
- DiMaio As far as we know the virus is transmitted by direct contact with another infected person. However, most people do not know they are infected, and as Linda said, these are very common infections and it is estimated that the lifetime risk for women is that about 80% will be infected by one of the cancer causing types. Most of them do not cause any problem, they go away, but she could still be transmitting the virus to somebody else.

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- Chagpar We have talked a little bit about this vaccine being primarily targeted to people before they become sexually active, but I can imagine that some of our audience may be sitting there and thinking, you know I am 40 years old and I am sexually active and they discover this vaccine now and it is too late for me to get vaccinated, I am still sexually active and I really do not want to get cervical cancer, head and neck cancer, or any other form of cancer.
- Niccolai There has been research looking into the safety and efficacy of the vaccine in women ages 27 to 45 and in fact it has shown some benefit in vaccinating those women. It has not been made a routine recommendation and my understanding is that this is due in part to cost effectiveness analyses. So, the amount of disease that you would prevent in that age group relative to what it would cost to vaccinate that age group makes it not cost effective from a public health point of view, but certainly an older woman, someone over the age of 27, could certainly talk to her provider and have a discussion about that and see what her options may be. I am aware of some older women who have been vaccinated. I guess that would be considered off label, but again it is up to a women to talk to her provider about her perceived risk and her sense of need for that vaccine. It is safe and effective for women in that age range.
- DiMaio Another point that perhaps is worth reiterating is that this vaccine has been given now in tens of millions of doses around the world and it seems to be an extremely safe vaccine. There are no documented severe side effects that have occurred for any of those women who have been vaccinated.
- Chagpar What if you know that you have HPV, you are an HPV carrier. You have been told that you have this. Does the vaccine help you at all?
- Niccolai Yes, it can. Again, there are multiple strains of HPV and there are four strains in the vaccine. So a woman who knows that she has HPV, maybe she had multiple infections, but possibly she only had one type of virus, and so she could be protected from infections with the other three types with the vaccine. In fact, a previous history of an HPV infection or a previous abnormal Pap smear is not a contraindication to getting the vaccine.
- Chagpar So then I guess it sounds like if you under the age of 27 and there are these routine guidelines at minimal side effects, great uptake in terms of preventing cervical cancer, preventing warts, preventing head and neck cancer, everybody should do this, particularly because in that younger population, this is covered by the majority of health plans and by federal programs. Let us say that you are over 27, one of the issues you pointed out is even if you had cervical issues and you have HPV, you can still benefit from the virus, but if you are over the age of 27, it may not be covered, is that right, because it is now off label?

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Niccolai That is correct.

Chagpar So how much does this cost?

DiMaio Again, as Linda said, it is three shots so it is about \$500 total for the three shot series, plus or minus a little bit.

Niccolai So it is expensive. That is certainly a problem for getting women vaccinated past 26, which is all the more reason why people that would like to be vaccinated should take full advantage of the coverage they have when they are adolescents or young adults and be vaccinated at that time.

Foss We are going to take a short break for a medical minute, please stay tuned to learn more information about HPV and cancer when we return.

*Medical  
Minute*

*There are over 12 million cancer survivors in the US right now and the numbers keep growing. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life changing experience. The return to normal activities and relationships may be difficult and cancer survivors may face other 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 comprehensive cancer centers like the one at Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has been a medical minute brought to you as a public service by Yale Cancer Center. More information is available [yalecancercenter.org](http://yalecancercenter.org). You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.*

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and we are joined today by our guests, Dr. Dan DiMaio and Dr. Linda Niccolai. We are discussing HPV and cancer, and right before the break Dr. Niccolai was telling us about how we can vaccinate against HPV and really have a significant impact on preventing cancer, which I think is such an exciting area. Can you tell us a little bit more about the data that we have, that shows vaccination really works? Has this been tried in other parts of the world? How much of an impact would this have if we were to take this and do it on a large scale?

Niccolai There has been, in the past year or two, some very exciting, very compelling data coming out from around the world showing early vaccine impact. Clearly cervical cancer takes decades to develop after infection, so we do not expect to see declines in cervical cancer in this timeframe, because the vaccine has only been out for about seven years, but we are already seeing dramatic declines in genital warts and in cervical infections, and in particular, in places like Australia and the United Kingdom where they have had very proactive vaccinations programs, they basically do school

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based vaccination programs for 11 year olds and 12 year olds, they have achieved very high coverage rates and in those settings the data coming out, articles were titled things like ‘The near Disappearance of Genital Warts,’ they are declining by 90%. We are also seeing some evidence in the US. In the US, we have seen some decline in genital warts and some decline in cervical infections. A very nice study came out from Cincinnati recently showing about a two-thirds decline in cervical infections in women who have been vaccinated from about 30% down to 10%. I am very encouraged that we are already seeing pretty dramatic affects, and again, if we can get those vaccination coverage rates up even higher, we can do even more.

Chagpar I am waiting for the headline that says, ‘The near Disappearance of Cervical Cancer’. Dan, we see a lot of cancers in the developing world as well and I read something recently that our audience may not be aware of, is that cancer is becoming a significant issue in the developing world with more cases than malaria and aids combined. Talk to us a little bit about vaccines in the developing world. Are they seeing an impact? Are they available there and what impact are they having there?

DiMaio You are correct that most virally induced cancers take place in the developing world, about 80% of all liver cancer, cervical cancer, and so forth are primarily more of a problem in Africa, parts of Latin America, and parts of Asia. Much more so than in this country, and that is because at least for cervical cancer, we have these effective Pap smear screening programs which have really had a major impact on the rate of cervical cancer. But the problem is that for HPV vaccination, it is not distributed widely in the developing world yet, because of its cost, but there is a lot of interest in hopefully bringing the cost down or changing the formulations so that more people can benefit from it, but right now the vaccine is being distributed widely only in the developed world. The hepatitis B virus, which is one of several types of hepatitis virus, there is a vaccine that has been around for 20 to 30 years, and now it is available quite cheaply and the majority of children in the world are vaccinated. So actually it is a tremendous step forward and we are also seeing drops in liver cancer because of the hepatitis B vaccination.

Chagpar Linda, one of the things you had mentioned with reference to Pap smears, and I just wanted to come back to this concept, is if you get vaccinated, does that mean that now you have prevented getting cancer? Can you still get cancer even if you have been vaccinated?

Niccolai Yes, you can, and one thing to be very clear about is that screening guidelines for cervical cancer have not changed for women who have been vaccinated, so whether you have been vaccinated or not, no matter how many doses you have gotten, no matter when you got them, and no matter what your vaccination status is, all women need to undergo cervical cancer screening in the same way. The reason for that is because again, there are multiple types of HPV in the vaccine, types 16 and 18, but there are 15 other HPV types that cause the remaining 30% of cancers. So women are not protected against some types that cause a smaller percentage of cancers. So routine screening

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remains the same for women who have been vaccinated, and it is interesting, the vaccine we have now protects against type 16 and 18. There is another vaccine that is in clinical trials right now. It is a nonavalent vaccine that protects against nine different types of HPV that are thought to cause about 90% of cervical cancers. So we expect those results to come out soon and that would be an exciting development, but even for that, again routine cervical cancer screening should remain the same.

Chagpar The idea is to get vaccinated and keep getting screened, but with that your rate of getting cancer will go down. So, hopefully most of those screens will come back and say Congratulations! You are negative.

Niccolai Exactly.

DiMaio Also, those women with those favorable results wouldn't need any further testing until the next Pap smear. So, a lot of follow-up testing we now to look at lesions will no longer be necessary because those lesions do not exist.

Chagpar Dan, one of the things I wanted to come back to, we opened the show by talking about viruses and cancer and I was impressed by how many cancers are caused by viruses, and you mentioned the hepatitis B vaccine, and how that has actually had an effect in lowering the rates of liver cancer. Are there other success stories with other kinds of cancer and other kinds of vaccines in the head, neck, or in other parts of the body where vaccines have been helpful?

DiMaio As I said, we expect that the HPV vaccine will prevent cervical cancer, will prevent some forms of anal cancer, vulvar cancer, penile cancer and some head and neck cancers. Hepatitis B vaccine is also very effective, and will prevent liver cancer. We do not yet have vaccines for the other human tumor viruses. There are now seven viruses known to cause cancer in people and people are working hard to try and develop those vaccines, but it is important to realize that most people infected by these viruses will never get cancer. For example, I mentioned that 80% of women will get an HPV infection and the vast majority will get better without the vaccine. The Epstein-Barr Virus is a virus that infects virtually everybody on earth and can cause cancer in a low number of people, there is no vaccine yet, but people are trying to develop a vaccine. And then HIV is an indirect cause of cancer because it causes immunosuppression, and people obviously are working on vaccines for HIV. We do not have them yet, but we have very effective anti-virals, so these anti-viral therapies will ultimately also reduce the risk of cancer in those patients.

Chagpar So Epstein-Barr Virus, is that the same virus that causes mono?

DiMaio Yes, the Epstein virus causes mononucleosis and also causes certain lymphomas and some Hodgkin's disease and possibly some stomach cancer. Most people though have a mild infection

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no worse than mono and sometimes they do not even know they are infected, as I said, about 90% or more of people, everybody on earth has been affected by this virus.

Chagpar So if you get mono, should you be scared that you are going to get cancer?

DiMaio No, absolutely not, as I said, almost everybody gets this virus and so you should just assume you are infected with Epstein-Barr Virus.

Niccolai It is similar with HPV where 80 million people in the United States are infected with HPV at any point in time, and about 12,000 women will develop cervical cancer every year which is 12,000 too many. So when we think about 80 million people that are infected, then the 12,000 who get cancer, you can see that the vast majority of people either clear HPV infections on their own, and they may have no symptoms. They may not even know they are infected and they will clear the infection. For a smaller number of women who do not clear the infection and go on to develop abnormalities in the cervix that are detected in their routine screening, those are easily treated with safe treatments, outpatient procedures, that remove the infected part of the cervix. So, yes, the good news is that the vast majority of people who are infected will not go on to develop cancer.

DiMaio The other good news is that it takes a long time to get the cancer. So, if you are infected and are unfortunate enough to develop cancer it is typically 20 years or more after the infection, so that is a lot of time to have Pap smear screening programs and to catch it at an early stage as Linda said, it is quite treatable and curable if caught at an early stage.

Chagpar I would bet you that there is going to be a person or two in our audience thinking in their contrarian way, and saying you know, you have got 80 million people who have this virus, only 12,000 of them are going to go on to get cancer. Why on earth would we vaccinate the 80 million? Why not just have them screened and then deal with the pre cancerous cells when they develop?

Niccolai Well again, the cancer and the precancerous cells are outcomes from an HPV infection but not all of the outcomes. So again, genital warts can be prevented. Genital warts are common and a million people every year get genital warts in the US. Those can be prevented with the vaccine and even the women who do not clear the infection and they may have some disease progression that can be detected and treated, that still is something to be avoided, because it involves multiple health care visits, multiple exams, multiple Pap smears, biopsies, lots of anxiety about health and difficulty in relationships. So preventing cancer is clearly the gold standard and the ultimate goal, but there are a lot of other diseases, other stages in our natural history that would be great to be avoided.

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- Chagpar You bring up a great point, which really speaks to the current era that we are in with health care costs being what they are. Can you talk a little bit about the cost effectiveness of massive vaccination programs like this?
- DiMaio Many people have done this sort of calculation and it has been concluded that just purely on economic grounds, that the cost of complete vaccination or complete enough that it will have a major impact, is several fold lower than the cost of our current screening and treatment procedures. So not even taking into account the emotional stress of having a positive test and the time that it takes to get it taken care of, just from purely a financial reason, it is a win-win situation.
- Chagpar So then the question, I guess being the contrarian, might be, well I get that that's great, let's vaccinate people. It is a cost effective strategy, given that the majority of people then would be prevented from getting this. Does it make sense then to extend the time period between Pap smears, so for example, if you are vaccinated instead of getting your Pap smear you know, every X number of years, you can make it every 2X. Has that been talked about or thought about?
- Niccolai Yes, it has been thought about and talked about a lot but nothing has changed for the screening recommendations for women depending on their vaccination status. The current guidelines are to begin screening for cervical cancer with Pap smear at age 21 and be screened every three years. At age 30, there is an option for women who have both the Pap smear and they are co-tested with an HPV test. If those are both normal they can go every five years. So the Pap smear looks for abnormal cells and the HPV test actually looks for the presence of the virus. So there is this new testing technology that can be used for woman over 30, but again, it does not depend on vaccination status and that may change, but it has not yet.
- DiMaio I think it is fair to say that we are all hopeful that as more and more women get vaccinated and as more and more men get vaccinated, we will be able to change the interval between Pap smears, but we are not there yet and the recommendations are the same. But my prediction is that that will change sometime in the future.

*Dr. Dan DiMaio is Waldemar Von Zedtwitz Professor of Genetics and Professor of Molecular Biophysics and Biochemistry and of Therapeutic Radiology. He is also Scientific Director and Deputy Director of Yale Cancer Center. Dr. Linda Niccolai is Associate Professor of Epidemiology and Microbial Diseases and Director of the HPV-IMPACT project in the emerging infections program. If you have questions or would like to add your comments, visit [yalecancercenter.org](http://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.*