TPWKY	This is Exactly Right.
Stephanie	My name is Stephanie, I am 34 years old, a soldier with the U.S. Army and also a government contractor. In 2016, right when I became a single mom of my two daughters, I went to get a pap smear. I'd only missed two pap smears before that and didn't think anything of it. The exam itself went as normal as possibly could be. It wasn't until about two weeks later that I got a call from the gynecologist herself urging me to come in as soon as possible. She offered to waive any copays and schedule me in between clients because she said it was absolutely urgent that I went in there. So I went in the very next day and she called me into her office and sat me down and I remember mostly how happy and cheery she was in what I knew was going to be very bad news. She took out a paper and started with a 'Don't panic, but we found cancer cells in your cervix.'
	And she explains that I had adenocarcinoma in situ, or AIS and explained to me that although they're considered pre-cancer cells, the cancer cell adenocarcinoma tends to jump membranes quicker than the other type of cervical cancer, squamous cell carcinoma. And she told me that I needed to schedule an appointment with the gynecologic oncologist at the hospital down the road. And the whole time she kept telling me not to worry, that this was good cancer, and that I am one of the lucky ones. I scheduled the appointment afterwards to go meet the oncologist and when I did meet him he said the same thing. He says I should feel really lucky and relieved, that this is good cancer and that they were going to watch me for a few months and schedule me for a cold knife conization biopsy.
	In those couple of months I had to basically learn how to deal with the possibility of having good cancer as opposed to bad cancer or no cancer. (laughs) And it was scary and because it was AIS I didn't get much support from the oncologist because as he felt, there were other graver cases of cancer that he needed to handle, which I didn't know any better so I thought it was fine. December 2016, right before Christmas, I went in for my cold knife colonization. The preop was way more serious than I thought it was going to be because I kept thinking good cancer, easy biopsy, and I would be out. But it was treated like a full surgery. After the surgery I was told that my margins were clear and that I was good to go and would need no more real oncologist help outside of a follow up appointment. Couple weeks after that I started getting really heavy cramping and bleeding during times that I was not on my menstrual cycle. And by April the pain became so severe I ended up in the emergency room.
	In the ER they ran a scan and they found a really, really small mass on the cervical canal and I had to go back to the gynecologic oncologist to see what we were gonna do next. The oncologist told me basically that the best case right now would be to have a hysterectomy. He actually wanted to wait a couple years to have the hysterectomy, not because the cancer wasn't serious but because he wanted to make sure that I was done having children. I have two daughters, they were 10 and 4 at the time and I felt different about that. He wanted to make sure that I didn't one day wake up and wanted to have a boy, a son. And I kept telling him that I was done having children so it was what I felt was an unfair battle I was having with my oncologist because I just wanted to get anything cancerous out of me so that I can, you know, be there for the children I do have. So after about a week I finally convinced him to just go ahead with the hysterectomy now.

	And so about two weeks after that ER visit I was in the operating room again having a hysterectomy. They took my cervix, my uterus, and my fallopian tubes and a little bit off the top of the vagina. And recovery was painful. I went into surgical menopause which was miserable for that short time that I was dealing with that. And the follow up appointment he said everything was great, there's no more sign of any cancer cells or any cancer anywhere and that I was clear to do annual pap smears for the next five years. So that was the first time that he told me that the cause of the cancer was actually HPV 16 strand. He had not mentioned it and neither had my gynecologist mentioned HPV up until that point and I think that has a lot to do with the stigma behind HPV and cervical cancer. And my last pap smear, which was I'm gonna say a few months ago, my gynecologist told me that she once again found HPV strand 16 around my vaginal cuff.
	So right now it's just being observed, hopefully it doesn't turn into any kind of cancer again. In the cervical cancer support group that I am in on Facebook I see women who have to do a lot of radiation and they have to use dilators so that their vaginas don't seal and they have to do chemo. And so I understand what my doctors were saying when they said I was one of the lucky ones even though I went from thinking I was totally healthy to two surgeries, ER visits, almost losing my job, losing my ability to ever have another child within 7 months I believe. So I do feel very lucky even though I know it was still a hard and traumatic event in my life. But there's not a day that goes by that I'm not thankful when I'm here and I'm hoping that this new or old HPV doesn't bring back the cancer in any way.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Wow, thank you so much for sharing your story, we really appreciate it.
Erin Allmann Updyke	Thank you.
Erin Welsh	Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	Yeah. I'm very excited for today's episode.
Erin Welsh	Me too. I mean, we say this every week and then we say that we say this every week but-
Erin Allmann Updyke	Listen. Today we're talking about HPV.
Erin Welsh	Yeah so we are reasonably excited.
Erin Allmann Updyke	Understandably excited.
Erin Welsh	This has been a long time coming. I feel like we've gotten a lot of requests about it. It's a big juicy one in that like there's a big biology to it, there's a big history to it, and I think I might be most excited for the current status type stuff.
Erin Allmann Updyke	Yeah cause that's a whole big... I feel like we're just gonna end up going on our own Erins's public health tangents about it all. (laughs)
Erin Welsh	Yep, I'll probably be on a high horse or like 'listen, here's the bottom line'. (laughs)

Erin Allmann Updyke	Exactly. So it's gonna be great, it's gonna be everything.
Erin Welsh	It's gonna be everything. But before we get to the meat of the episode, we've got some business to take care of.
Erin Allmann Updyke	It's quarantini time!
Erin Welsh	It is quarantini time. What are we drinking this week?
Erin Allmann Updyke	Well of course we're drinking the Pabst Schmear.
Erin Welsh	(laughs)
Erin Allmann Updyke	I feel like I didn't say that great.
Erin Welsh	So I've been not practicing but every time I say it I realize, am I enunciating Pabst clearly enough?
Erin Allmann Updyke	Pabst.
Erin Welsh	Like Pabst... Maybe we should just explain what's in it and then it might be easier to hear the pronunciation.
Erin Allmann Updyke	It's PBR, Pabst Blue Ribbon, and grapefruit juice and some simple syrup.
Erin Welsh	Yeah.
Erin Allmann Updyke	Because it's like a pap schmear, get it?
Erin Welsh	Pap schmear. So this, just like Cold As The Rocky Mountain Spotted Fever, was one of the quarantini names that we came up with on the day that we came up with the podcast.
Erin Allmann Updyke	It was one of the clinchers, like we have to make this podcast because it's too good of a name to let it go to waste.
Erin Welsh	I still think of, like even before recording this, I would still think of Pabst Schmear whenever I drank a PBR. (laughs)
Erin Allmann Updyke	(laughs) I thought of it every time I got a pap smear. Ayo!
Erin Welsh	Ayo! Well we will post the full recipe for the quarantini as well as the nonalcoholic placeborita on our website thispodcastwillkillyou.com as well as on all of our social media channels.
Erin Allmann Updyke	Absolutely. Do we have any other business before we dive into this big episode, Erin?
Erin Welsh	There's usual stuff. There's fantastic, wonderful, beautiful merch. There is a bookshop.org affiliate account and also there is a Goodreads list where we add the books that we read and also it's like a nice community list where listeners add books that they think are of the podcast or related to the podcast.

Erin Allmann Updyke	Yeah. Okay. Well then let's take a quick break and then dive into this episode.
Erin Welsh	Sounds great.
TPWKY	(transition theme)
Erin Allmann Updyke	So HPV. HPV stands for human papillomavirus. This is a double-stranded DNA virus except it's not just a virus, right?
Erin Welsh	Oh no.
Erin Allmann Updyke	This is an entire family of double-stranded DNA viruses, the papillomaviruses which include I don't even know how many viruses but viruses that infect essentially, I don't know, every animal ever. Every mammal that we've ever looked at, birds, turtles, snakes, fish, I think every animal.
Erin Welsh	Fish, that's the one that really got me. I was like, fish?
Erin Allmann Updyke	Yeah, fish. I had an advisor who studied turtle papillomaviruses.
Erin Welsh	Oh cool.
Erin Allmann Updyke	Yeah. But today we're talking about the human papillomaviruses, aka HPV. So for HPVs, these are a group of several hundred viruses which fall into a few large kind of subgroups, they call them alpha, which is the one that we're gonna focus on the most today, as well as beta, gamma, delta, there's mu, there's nu, there might be a chi. There's a lot of different subgroups of these viruses. And then within each of these different subgroups there are dozens of different types of HPV which we're probably all familiar with, you've probably all heard at some point or another a type of HPV, HPV 16, HPV 6, 11. On top of that and kind of within these larger subgroups you can also bin these different HPVs based on the types of cells that they tend to infect.
	So all HPV viruses infect epithelial cells which are the cells that make up our outer linings of everything in our body. But we have a lot of different types of epithelial cells on our skin, the linings of our respiratory tract or our GI tract or our genital tract. So you can also look at these HPV types as some being more likely to affect the skin, which they sometimes call cutaneotropic, like cutaneous like your skin. These are the strains or types that tend to cause warts of all different kinds. Right, everyone knows warts.
Erin Welsh	Oh okay. Mm-hmm.
Erin Allmann Updyke	But then there are also the mucosatropic types which preferentially infect cells of our mucosal lining, like the cervix which is gonna be what we talk the most about today, but also the anal canal, our oropharynx. These can also cause warts, generally of the genital tract or even in our larynx or pharynx. And so in general it's these HPV types that we're going to focus on for this episode. All of these tend to be in the alpha HPV category. It gets a little bit more complicated because on top of that you also have high risk and low risk strains or types.
Erin Welsh	I'm very excited to learn more about this.

Erin Allmann Updyke	Yeah. And that's because that's the biggest story in association with HPV and that is the risk of cancer. So when we say high risk, these are HPV types that have a high risk of potentially causing cancer and low risk means they have a very low risk of potentially causing cancer. All right, so let's talk about how these viruses are transmitted. A lot of times we think of HPV as a purely sexually transmitted disease. And many types are sexually transmitted diseases and those cause genital warts and those types also are associated with certain cancers. But there are so many different types of HPV and really when it comes down to it, they're all transmitted by contact. So sexual contact but if you have HPV on your hands then you can transmit it from hand to anything, if you have plantar warts, which are warts on the bottom of your feet, those actually shed so much HPV that that can end up on the floor and it can live for a really long time and then someone else can walk along that floor and get HPV from the floor.
Erin Welsh	How long is a long time?
Erin Allmann Updyke	I think I read months potentially but I don't know under what conditions that would be true.
Erin Welsh	Wow.
Erin Allmann Updyke	Yeah. All right. But basically if you include all these different types, all these different subgroupings of HPV, it's really everywhere. Like this is such a ubiquitous virus family.
Erin Welsh	Oh yeah.
Erin Allmann Updyke	And it's quite transmissible. If we look more at sexually transmitted HPV or if we look just specifically at sexually transmitted HPV, it's estimated that the per sexual act transmission rate is up to 60%.
Erin Welsh	Wow, yeah. I mean the thing is like by the time you're a couple of years old, you are probably infected with one HPV, right?
Erin Allmann Updyke	Right. What kid doesn't have warts at some point in their life? Like everyone has at least a wart.
Erin Welsh	Right.
Erin Allmann Updyke	But let's get one thing really clear right off the bat. The vast, vast majority of HPV infections are almost entirely benign. Even if they present with a wart which not all of them do, in general over 90% even of genital HPV infections will be cleared completely. Especially in younger age groups like teenagers and young adults. This process is not super fast, the half-life of the disease, which it's interesting to talk about a disease having a half-life because we don't usually do that.
Erin Welsh	Yeah.
Erin Allmann Updyke	But that tells you just kind of how long you can end up infected with this and yet still clear it. But the half-life for HPV is thought to be like 8-10 months. So almost all infections will clear in about a year or two.
Erin Welsh	And so is an infection defined as actively shedding virus and then like at the end of that infection the virus is cleared from your body, your immune system has taken care of it?
Erin Allmann Updyke	Yes, cleared means that your immune system has taken care of it and you no longer have virus in your cells.

Erin Welsh	Okay. And are you shedding that entire time or not?
Erin Allmann Updyke	That's a good question. As far as I believe, I believe yes.
Erin Welsh	Okay.
Erin Allmann Updyke	I would guess that how much virus you shed probably varies throughout that time of course.
Erin Welsh	Okay.
Erin Allmann Updyke	But not every infection is cleared. So some types of HPV can cause a more latent infection where they essentially can stay in our cells for a longer time and over that time period end up causing cancer. HPV is associated with essentially 100% of cervical cancers.
Erin Welsh	Right, right.
Erin Allmann Updyke	As far as we can tell so far, cervical cancer, it is necessary to have an HPV infection in order to have cervical cancer, it's not the only thing but it is a necessary part of the cervical cancer process. However HPV infection is also associated with vaginal cancer, vulvar cancer, penile cancer, anal cancer, oropharyngeal cancers, and laryngeal cancers, so that's of the back of the throat and the throat.
Erin Welsh	I think it's interesting because that is not a commonly known thing or it's not something that was commonly spread as part of the public health message.
Erin Allmann Updyke	Oh Erin.
Erin Welsh	(laughs)
Erin Allmann Updyke	I have so many thoughts about that that we'll touch on in the current events section.
Erin Welsh	All right, we'll step down from the platform for the time being.
Erin Allmann Updyke	Yeah. For the time being. Let's get back to our HPV. So the real question of course is how on earth can a virus cause cancer?
Erin Welsh	Yeah.
Erin Allmann Updyke	Right. And the answer is so fascinating, especially because we have talked about a virus that causes cancer previously but in a totally different way.
Erin Welsh	Hep C?
Erin Allmann Updyke	Hep C, right. This is totally different. Okay so to understand this we have to understand HPV and then we have to understand our epithelial cells a little bit. So let's get into it. We know that because this is a virus it has to infect our cells in order to replicate, since viruses use our cellular machinery in order to replicate. So HPV enters into our tissue via little microabrasions, so you have to have small, tiny little cuts on your skin or mucosal membranes in order for HPV to get in. And then it infects a very specific set of our epithelial cells. It infects the basal layer, that's the bottom layer of our epithelial cells.

	So think of this like if you look at a cross-section of your skin, you have all the dead skin cells on top that slough off when you wipe or wash or whatever, and then you have other layers of cells that are like differentiated and they're doing their thing. And then at the bottom, what we have here are these kind of stem cells, these basal cells are the ones that replicate over and over and then produce all of these top layers, they kind of push themselves up if that makes sense.
Erin Welsh	Huh. Okay. Yeah.
Erin Allmann Updyke	Okay? So that bottom layer is where HPV infects.
Erin Welsh	Interesting.
Erin Allmann Updyke	Mm-hmm. Once they're there, once HPV is in those cells, first the virus will use our cell machinery to replicate a few times just so there's like a nice group of them in each cell, like maybe 50 to 100.
Erin Welsh	Okay.
Erin Allmann Updyke	And then these viruses have a couple of proteins that act to help stimulate our cells to replicate. So epithelial cells like our skin cells, they generally replicate pretty rapidly already compared to a lot of cells in our body but this HPV infection is like, 'Hey, let's kind of do this even more.' Because every time the cell replicates, it's going to replicate all that viral DNA as well.
Erin Welsh	That's an interesting strategy instead of like... Cause usually we see viruses invading, replicating in the cell, and then bursting the cell, killing it.
Erin Allmann Updyke	Yes.
Erin Welsh	And then infecting another cell and another cell and another cell and doing the same thing. But this is like contained replication.
Erin Allmann Updyke	Yes, Erin! You're right.
Erin Welsh	Ooh.
Erin Allmann Updyke	Isn't it exciting?
Erin Welsh	This is very interesting.
Erin Allmann Updyke	So if this happens on our skin or on some of our mucosal surfaces, with most of these HPV types it might manifest as warts, right. So warts are basically just keratinocytes, our skin cells that kind of grow, they get like extra keratinized and then as those cells slough off, that's when the virus explodes out and is able to go on and infect other cells.
Erin Welsh	That is really interesting.
Erin Allmann Updyke	Yes. But that doesn't tell us, what about cancer? That's not cancer. That's warts. So there's another thing that certain types of this virus have that allow them to be even sneakier. So the high risk subtypes have a few extra tricks. One is that they can actually integrate into our genome directly.

Erin Welsh	That's spooky, yeah. It happens.
Erin Allmann Updyke	Isn't it? I love it.
Erin Welsh	(laughs)
Erin Allmann Updyke	So that means that they can do an even better job of disrupting our normal cell functioning because they actually can insert themselves inside our genome, like inbetween our DNA. It's like human, human, HPV, HPV, human, human, right. On top of that the high risk subtypes have a couple of extra proteins, one that's called E6, one that's called E7, maybe also E5, and what these proteins do... So we already know that HPV has these proteins that tell our cells, 'Hey replicate more than you want to.' These other proteins on tops of that function to suppress a couple of genes that we have in our bodies which are called p53 and pRB, or polio retinoblastoma, which in our normal human cells are called tumor suppressor genes.
	These genes are responsible for doing like a double check. Whenever our cells replicate DNA these proteins, the proteins that are encoded for by these genes, they're like, 'Hey hey. Let's take a minute real quick. You guys, you made a mistake here. This isn't right. You can't do that. This needs to either be fixed or I'm gonna kill you.' (laughs) So it either stops DNA replication or they try and fix it. And if they can't do that then they just do apoptosis and they're like, ' Scratch this whole operation, this cell's out of commission.'
Erin Welsh	Right.
Erin Allmann Updyke	So these tumor suppressor genes are what prevent our cells from replicating out of control and what prevents our cells from replicating incorrect faulty DNA sequences. High risk HPV turns this function off. So not only is HPV convincing our cells to replicate more rapidly, but as they do so, they replicate incorrect and messed up DNA which can lead to eventually, you know how these cells are in the basal layer, the bottom layer of our skin?
Erin Welsh	Yeah.
Erin Allmann Updyke	And normally skin cells replicate up, up, up. This uncontrolled incorrect division can allow them to invade beyond the basement membrane which is the layer underneath those basal cells and invade deeper structures. That's cancer.
Erin Welsh	And is that primarily in the mucosal or only mucosal?
Erin Allmann Updyke	Yeah, so this is what happens in the high risk HPV subtypes which tend to infect mucosal surfaces.
Erin Welsh	It's so interesting to me because like from a virus' point of view, this seems like an excellent strategy.
Erin Allmann Updyke	Yeah. It's such a good strategy.
Erin Welsh	So like why don't we see this more, I guess?
Erin Allmann Updyke	I think it's very, very complicated.

Erin Welsh	It must be.
Erin Allmann Updyke	Yeah because it's not just that this virus itself is growing really rapidly. Like this virus has to have a very intimate relationship with our genome. So it has to have evolved with us for a very long time, I would guess, I actually didn't look into the... You're gonna talk a little bit about it, I think but-
Erin Welsh	I'm thrilled, this is so great. I love when this happens, yes.
Erin Allmann Updyke	(laughs) But yeah I mean that's what that would suggest, right? Because it has such an intimate relationship with our genes. It specifically is turning off these tumor suppressor genes and like you said, it's a great strategy because now this virus can invade our whole body. Cancer can go anywhere it wants once it starts going.
Erin Welsh	How does it disrupt p53?
Erin Allmann Updyke	Oh gosh Erin, don't ask me that.
Erin Welsh	Okay. It just does. (laughs)
Erin Allmann Updyke	(laughs) Yep. That's what I have for the pathophysiology of this disease.
Erin Welsh	It's very fascinating and it's very scary.
Erin Allmann Updyke	Mm-hmm. Mm-hmm.
Erin Welsh	Cervical cancer is the one that we hear the most about.
Erin Allmann Updyke	Yeah.
Erin Welsh	Why is that? Well first of all, why are those areas so much more susceptible to cancer caused by HPVs and why cervical cancer most of all? Or is it just that we hear more about it?
Erin Allmann Updyke	It's a good question. I think in part we do hear more about it and we'll talk about kind of why that is and part of that's cause we can screen for it, which is great. It's also I think because other cancers that are associated with HPV also have other risk factors or other things that can cause them without necessarily having HPV. Whereas cervical cancer, it seems that HPV is a necessary precursor, like if there's not HPV< the cervix is never going to become cancerous.
Erin Welsh	Okay.
Erin Allmann Updyke	If that makes sense.
Erin Welsh	Yes, that is interesting.
Erin Allmann Updyke	Yeah. The cervix by the way is the bottom part of the uterus. Some people might not know that.
Erin Welsh	(laughs) It's very true.

Erin Allmann Updyke	Yeah. It's the bottom part of the uterus, it looks... So I guess we'll talk about this so that we can understand why we're able to screen for cervical cancer. And I think Erin, you'll talk a little bit more too about like how someone came up with this?
Erin Welsh	Oh yeah.
Erin Allmann Updyke	Yeah. So it's the bottom part of the uterus which is also if you are looking into the vagina, it's the very top part of what you'd see at the vaginal canal. It looks like a little donut, it's kinda cute, with a little hole in the middle. That little hole in the middle goes up, like through that hole would go up into the uterus. And at that zone right in the middle of that hole is where the outside body meets the inside body and there's a transition zone in there where our cells change type. That transition zone is also very susceptible to HPV infection.
Erin Welsh	Huh.
Erin Allmann Updyke	The same is true we think of the transition zone, cause there's a similar transition zone in the anal canal where we go from outside of the body to the inside of the body. And that transition zone in the anal canal is also very susceptible to HPV infection.
Erin Welsh	So the transition zone, so you have cells turning into different kinds, that's sort of the border.
Erin Allmann Updyke	Right, yes.
Erin Welsh	Does that have something to do with it? Just the fact that there are like different instructions and so a different type of cell might not receive the same amount of scrutiny?
Erin Allmann Updyke	Yeah, it's possible.
Erin Welsh	Okay.
Erin Allmann Updyke	So I think from what I have read, we don't fully understand exactly that process. But it is thought that yes, something about that transition zone and the kind of, what's called metaplasia or cell type change that happens there might have something to do with why the cervix.
Erin Welsh	Interesting. Interesting.
Erin Allmann Updyke	Right? But the good news when it comes to cervical cancer at least is that it's a really preventable type of cancer. At this day and age it's a very preventable type of cancer, at least in theory. We can prevent it in a number of different ways. One is by - this is kinda fun cause we can talk about the types of prevention, right?
Erin Welsh	Yeah.
Erin Allmann Updyke	So in public health we have a lot of different types of prevention. And one is called secondary prevention and that's what screening is. So that means we're trying to find precursors of something like cancer or very, very early cancer that we can treat before it becomes severe disease. So screening like breast cancer screenings or cervical cancer screenings are secondary prevention. And we can do that, we can scrape off cells at that transition zone from the inside of the cervix and then look at them under a microscope and look for precancerous changes. And that can tell us, 'Hey, you're at risk of having cancer.'
Erin Welsh	Right.

Erin Allmann Updyke	And then you can go one step further and do a second test where you basically put acetic acid on the cervix and look with another type of special lens to see if there are any changes and then remove those as well before they become cancer or before they become invasive cancer.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	So that's one type of screening and that's the pap smear combined with what's called colposcopy, which is the more invasive test. Nowadays we have another type of screening which I get very excited about cause it's a lot less invasive, it doesn't have to be done as often, and it's as good if not better and that is direct HPV testing. So because cervical cancer necessarily has HPV infection, you can test cervical cells really like just a vaginal swab, it doesn't have to be all the way jamming into the cervix, which is a lot more painful, and you can just test for the presence of certain types of high risk HPV. And then if you see it, then you go from there in terms of what you do about it. So that's really exciting because that's secondary prevention that's possible. But even better than secondary prevention is primary prevention.
Erin Welsh	Oh yeah.
Erin Allmann Updyke	Primary prevention means preventing somebody from ever getting a disease in the first place. And for cancer we often can't do that. So for cancer, secondary prevention is often kind of like the mainstay of public health prevention, that's usually all that we can do is try and find it early and do something about it. But for cervical cancer, we can prevent it because we have a vaccine.
Erin Welsh	It's amazing.
Erin Allmann Updyke	It's amazing. We have a cancer-preventing vaccine.
Erin Welsh	I know. We're living in the future.
Erin Allmann Updyke	We really are. So there are three different types of HPV vaccines that are currently licensed. One covers four types of HPV, two that are high risk which are 16 and 18, those cover 70% of all cervical cancer in the world; as well as 6 and 11 which cause about 90% of genital warts, which is awesome.
Erin Welsh	Mm-hmm. Yeah.
Erin Allmann Updyke	There's another one that was licensed a couple years later that only covers 16 and 18, so it doesn't protect against genital warts but it does protect against 70% of cervical cancers. But recently in the last couple of years, there's another one that covers nine strains including 16 and 18, which are the most common causes of cancer, but also 31, 33, 45, 52, 58, which are all high risk types that altogether account for 90% of all cervical cancers.
Erin Welsh	That's amazing.
Erin Allmann Updyke	And then it also covers genital warts. We'll talk about all of the pitfalls with this vaccine and with screening in general a little bit more later on in this episode. But first, Erin.
Erin Welsh	Ooh!
Erin Allmann Updyke	Where did we... How did we... What is this virus? This cancer virus? Like what?

Erin Welsh	I know, I know. I'm very excited to talk about it. Let's take a quick break first.
TPWKY	(transition theme)
Erin Welsh	So first off, to say that papillomaviruses in general have been around since humans became human would be a bit of an understatement.
Erin Allmann Updyke	(laughs)
Erin Welsh	Kind of an enormous understatement, actually. Because papillomaviruses are thought to be hundreds of millions of years old.
Erin Allmann Updyke	Have they been around since viruses were viruses? (laughs)
Erin Welsh	I mean not far off. The number and diversity of hosts that they infect, like you mentioned Erin, fish, birds, mammals, reptiles, etc and also their diversity within the host species, it just like highlights how ancient this group of viruses is. All right, so I found one paper that puts the root of the papillomavirus tree back to 424 million years ago.
Erin Allmann Updyke	What?
Erin Welsh	Like this is beyond anything that we've talked about in terms of ancient-ness.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. And then the first big divergence was around 184 million years ago and that was during the period when mammal evolution and diversification led to the development of a whole lot of new real estate for these viruses. Specifically some of the mammalian skin characteristics like hair, sweat glands, sebaceous glands, milk glands, etc. So this is just like open space to occupy.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	Tons.
Erin Allmann Updyke	New territory.
Erin Welsh	Absolutely. And so from that point there are several other additional diversification events or periods where the papillomavirus diversity kind of like fanned out even further but I'm just gonna leave it at that because it gets sort of like 'and then, and then, and then.' Basically the bottom line is that papillomaviruses are incredibly old and have evolved with their hosts and that the cancer-causing genes in papillomaviruses are not specific to human papillomaviruses and so it's likely that those genes evolved before humans did.
Erin Allmann Updyke	What?
Erin Welsh	So like those genes are likely similar across all of the like different animal viruses.
Erin Allmann Updyke	Honestly that makes sense because p53 is highly conserved.

Erin Welsh	Exactly. Exactly, so it's probably not like convergent evolution, I would guess anyway. Also because of the complexity, but whatever
Erin Allmann Updyke	(laughs)
Erin Welsh	(laughs) And because of how old and widespread these viruses are, it probably doesn't surprise you to learn that there are lots and lots of ancient writings about them or at least about the things that they caused. Like warts. Genital warts, for instance, have been written about since at least the time of Hippocrates, so like 460-370 BCE, and the medical term for them, condylomata acuminata, comes from the ancient Greek and Latin. Condyloma meaning knob or round tumor and acuminata from the Latin for sharp points. And a term for plantar warts, myrmecia, comes from the Greek word for anthill.
Erin Allmann Updyke	Oh, I can see that.
Erin Welsh	That's fun. And in Ancient Rome, genital warts were called ficus or thymus because apparently they looked like an open fig or resembled the leaves of the thyme plant. Yeah. And besides just writings about warts, there was also a toe wart found on the embalmed body of an Ancient Egyptian worker from like thousands of years ago. But you know, like all types of warts, the warts coming on fingers, genital warts, plantar warts, they all made appearances in Ancient Rome and Greek medical texts and it was commonly assumed that sexual activity, particularly excessive sexual activity was the cause of genital warts.
Erin Allmann Updyke	(whispers) Excessive.
Erin Welsh	The causes of other warts like those commonly found on fingers were often chalked up to females addicted to "solitary habits" in quotes, aka...
Erin Allmann Updyke	(laughs)
Erin Welsh	Do you know what I mean by that?
Erin Allmann Updyke	Oh I know what you mean by that.
Erin Welsh	Okay. And also those that regularly were hen testers, so they would stick their finger up the cloaca of a hen to see how close it was to laying an egg.
Erin Allmann Updyke	Oh my god. I have never thought about a finger going up a cloaca. I don't like the thought of it. (laughs)
Erin Welsh	(laughs) I hope that won't become an intrusive thought for you.
Erin Allmann Updyke	I think it might, yeah.
Erin Welsh	Well you know, there are worse things.
Erin Allmann Updyke	Mm-hmm.

Erin Welsh	(laughs) So anyway, the precise cause of warts was not known, like the fact that they were viral but they were recognized to be contagious. But for the most part, this early focus on warts wasn't so much on uncovering the cause of warts but rather how to treat them or get rid of them. Which brings me to one of my favorite things which is old-timey cures.
Erin Allmann Updyke	Oh I feel like it's been a very long time since we've discussed old-timey cures!
Erin Welsh	I feel the same way and so because of that I have quite a big section on this. (laughs)
Erin Allmann Updyke	(laughs)
Erin Welsh	Cause I was like, oh let me find my favorites and I'll put them in here and I just kept adding more so... And I'll link to papers that have even more. So this is like specifically old-timey folklore of Europe in terms of how to get rid of warts.
Erin Allmann Updyke	Okay. All warts or genital warts?
Erin Welsh	Some of them didn't specify but for the most part it seemed like skin warts, like finger, toe, whatever.
Erin Allmann Updyke	Okay, okay. All right.
Erin Welsh	Because I mean some of them it's very clear that it's not genital warts, but yeah.
Erin Allmann Updyke	Oh okay. Oh dear.
Erin Welsh	(laughs) Okay so these can be grouped into the following categories. One was transference, so like transferring your wart to somebody else or something else. Number two was animal, plant, or mineral remedies. Number three was prayers or incantations. And number four was miscellaneous, things like crossroads, moon phase, funerals, etc.
Erin Allmann Updyke	What? Okay.
Erin Welsh	Yeah, I'll get there. Okay so a couple examples of transference. You should rub the warts against a man who is the father of an illegitimate child without his knowledge.
Erin Allmann Updyke	(laughs)
Erin Welsh	(laughs) So that one you'd probably just want to do with hand warts, right? I don't think you could do genital warts.
Erin Allmann Updyke	Yeah no. Not without his knowledge.
Erin Welsh	Nope. And then quote: "If a bag containing as many small pebbles as a person has warts be tossed over the left shoulder, it will transfer the warts to whoever is unfortunate enough to pick up the bag."
Erin Allmann Updyke	(laughs)

Erin Welsh	Another one, quote: "Take one of the large black snails which are to be found during summer, rub it over the wart, and then hang it on a thorn. This must be done nine nights consecutively, at the end of which the wart will completely disappear." You could also rub your wart with a piece of bacon, cut a slit in the bark of an ash tree and slip the bacon under the bark, and then repeat the words "ashen tree, ashen tree, pray by these warts of me." And then you stick a pin into the tree, and then into the wart, and then back into the tree. And then your wart's gone!
Erin Allmann Updyke	Of course it is.
Erin Welsh	And there was also, if those didn't work, there was also the option of having someone buy your wart off you. I guess there was like an open market for that. Or you could treat it with any one of the following, so like fish heads, pig's blood, lizard's blood, menstrual blood, dove's tongue, tobacco juice, and fasting spittle.
Erin Allmann Updyke	Okay.
Erin Welsh	I mean honestly I could go on and on with more wart remedies. Catch a long-horned grasshopper and have it bite off your wart directly, so they were known as like a wart-biting grasshopper or something.
Erin Allmann Updyke	Of course.
Erin Welsh	It's not a great solution now because the grasshopper species Decticus verrucivorus is endangered, so don't do that.
Erin Allmann Updyke	Oh dear. Don't do that.
Erin Welsh	And then finally, spit on your wart and rub it three times in the direction of a passing funeral while saying, "My wart goes with you." When I read that Erin, all I could think of was, 'My wart be with you, and also with you.' (laughs)
Erin Allmann Updyke	And also with you. (laughs) Oh yeah.
Erin Welsh	So some good ones there. There are many more.
Erin Allmann Updyke	That's the title of the episode.
Erin Welsh	My wart be with you? Excellent.
Erin Allmann Updyke	Mm-hmm. and also with you. (laughs)
Erin Welsh	(laughs) Anyway okay, I should move on though. So from ancient times to around the late 1800s, warts remained a nuisance for many people, hence these innumerable cures described. But little progress had been made in terms of understanding the transmission of warts or their viral cause. But it was around this time that things changed. So the development of germ theory and microscopes allowed more close examination into the contagiousness of these warts as well as to what they looked like at a cellular level, like what was going on. And in 1893, a French dermatologist made the observation that genital warts and common skin warts might be the same thing or caused kind of by the same thing. And other doctors successfully gave themselves warts. So they were like, 'Oh, I'll try this out. I'll try to put some wart juice on me.'

Erin Allmann Updyke	Like they gave themselves skin warts from someone's genitals to test it?
Erin Welsh	Well so that was mostly skin to skin. But then in 1906 there was a major breakthrough when an Italian doctor made an extract of genital warts and then passed it through a filter that would leave out any bacteria or fungi and then he injected this wart juice into his skin, where warts later developed.
Erin Allmann Updyke	That is some commitment right there.
Erin Welsh	It is. And this led to two important pieces of information. One was that warts are probably caused by a filterable, transmissible agent, aka virus. And it also showed that genital warts and skin warts were caused or could be caused by the same virus.
Erin Allmann Updyke	Right.
Erin Welsh	The virus itself that caused the warts or any human papillomavirus wouldn't be discovered until 1950.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. But in the meantime there were a couple of other important developments. So I'm gonna shift gears for a little bit and talk about cervical cancer.
Erin Allmann Updyke	Ooh.
Erin Welsh	In the early days of cancer research, it probably seemed like with every new thing you learned, you probably had ten times the amount of questions you started out with. Cause there didn't seem to be a single unifying cause of cancer or even predictability within the same type of cancer. New cancers were being discovered all the time, like it seems like an utterly chaotic field in that sense.
Erin Allmann Updyke	Oh man, I still feel like that.
Erin Welsh	Yeah, absolutely. And then in 1910, a key piece of research seemed like scientists were getting closer to at least one solid answer because that year a pathologist named Peyton Rous described how he was able to induce malignant tumors in healthy chickens by injecting them with a filtrate from malignant sarcomas in sick chickens. In other words, Rous discovered the first cancer-causing virus in 1910.
Erin Allmann Updyke	Whoa. 1910?
Erin Welsh	1910. Like not only was this super exciting but it was also a very important development in our understanding the nature of viruses and cancer. And Rous was awarded a Nobel Prize in 1966 for the finding, which I think is the longest actually delay between work and award in Nobel Prize history.
Erin Allmann Updyke	Wow.
Erin Welsh	After the Rous sarcoma virus was discovered, many other researchers began looking into possible infectious causes of cancers. And one of these researchers was Richard Shope, who's name may sound familiar because he was one of the people who discovered the Influenza A virus and linked it to the 1918 influenza.

Erin Allmann Updyke	Oh gosh. That was literally 3.5 years ago, I do not remember his name. Sorry.
Erin Welsh	I know. Well but his name might also sound familiar because his son Robert Shope was a famous virologist who worked on arboviruses mostly and discovered more novel viruses than anyone else previously.
Erin Allmann Updyke	Wow.
Erin Welsh	Like unbelievable amount of virus research, he was like a walking encyclopedia apparently.
Erin Allmann Updyke	Wow.
Erin Welsh	Anyway, Wikipedia rabbit hole. (laughs)
Erin Allmann Updyke	(laughs)
Erin Welsh	Speaking of rabbits, in the 1930s Shope, who had collaborated with Rous, was out hunting one day in Iowa when he noticed what looked like a wild cottontail rabbit with horns. These rabbits, these horned rabbits were a strange thing to see but they weren't unknown. Like there was already sort of this... First of all, everyone who was a hunter out there was like, 'Oh yeah we see those all time.'
Erin Allmann Updyke	Yeah they're the jackalope.
Erin Welsh	Secondly, there's the jackalope. It's actually thought that these horned rabbits might have given rise to the jackalope myth.
Erin Allmann Updyke	Yes! That's awesome!
Erin Welsh	It's very cool. So Shope trapped some of these rabbits so he could get a closer look at their horns and discovered that the horns were actually cancerous growths caused by a rabbit papillomavirus.
Erin Allmann Updyke	What?
Erin Welsh	Yeah. So the jackalope is just a rabbit infected with a cancer-causing papillomavirus.
Erin Allmann Updyke	Poor jackalopes! Oh gosh.
Erin Welsh	And he was able to in the lab induce these cancers in other rabbits through like passing on the virus.
Erin Allmann Updyke	Wow.
Erin Welsh	And I also realized I haven't done the etymology for papilloma, which comes from a combo of Latin and Greek words that together mean 'a tumor resembling a nipple'. So there you go. (laughs)
Erin Allmann Updyke	(laughs)

Erin Welsh	Just gonna leave that there. And then the final big piece of news or developments happened in 1964 which is when the discovery of the Epstein-Barr virus and the fact that it could cause Burkitt's lymphoma showed that cancer-causing viruses didn't exist solely in animals but could also cause cancer in humans.
Erin Allmann Updyke	Mm-hmm, mm-hmm.
Erin Welsh	Okay so at this point all of the pieces were in place to link HPV to cervical cancer but that didn't happen right away. And in order to tell that part of the story, I want to dive a bit into the history of cervical cancer to give a bit more context. Cervical cancer doesn't leave any marks on the skeleton so we have to rely on early descriptions of what we might think might be cervical cancer to understand sort of the perception of the disease as well as to guess how long it's been around. Although given how ancient these viruses are how like everyone is infected with them, it's safe to assume that cervical cancer has been in humans from day one. Although one of the papers I read noted that the rate of cervical cancer probably increased over time, not due to human travel or increase in population density which might have had a role to play, but due to the nature of cancer in general as a disease of longevity.
Erin Allmann Updyke	Yeah.
Erin Welsh	So like when life expectancy was lower, people were more likely to die of something else before getting cervical cancer.
Erin Allmann Updyke	Yeah it's a long time period from infection to cancer for cervical cancer, so it makes sense.
Erin Welsh	Yeah. And there are some ancient writings, Ancient Egyptian papyri and some Hindu manuscripts from like the 4th Century BCE, and then also in Ancient Rome there was a device uncovered that looks like a very early speculum, which is pretty interesting to think about. Like the 1st Century CE.
Erin Allmann Updyke	Ugh. I bet it's painful.
Erin Welsh	Oh yeah. And it's gonna get a lot more painful I think.
Erin Allmann Updyke	Yeah.
Erin Welsh	Because early treatment for ulceration or malignant growth of the uterus or cervix was usually something along the lines of cauterization or partial removal. But honestly those things usually ended up leading to just a quicker death. By the 1600s/1700s or so, people had started to make the distinction between malignant and benign in these uterine or cervix tumors. But the distinction was pretty much useless because it generally involved the doctor just going, 'Okay, this patient is wasting away and dying so this must be malignant.' Or 'This tumor doesn't seem to be changing at all, so the patient's probably fine.'
Erin Allmann Updyke	Great.
Erin Welsh	Yeah. Essentially doctors were just sitting around waiting for their patient to die or not. As you might have guessed, many doctors were not especially content with this type of hands=off medicine and so they began to explore treatments such as belladonna, hemlock, strychnine, lead, mercury, etc. Basically like any very toxic, intense compounds.
Erin Allmann Updyke	All kinds of things that can kill you.

Erin Welsh	Mm-hmm, mm-hmm. And of course nothing worked and the birth of the field of gynecology didn't exactly help things either right away. Gynecology began to be recognized as a separate distinct medical field around the 1700s/1800s but not to gather knowledge that would improve the health of women everywhere, but rather to detect sexually transmitted diseases in sex workers. Basically a big part of the push for gynecology was to protect the male clients of sex workers. Like you were given a clean bill of health and allowed to work or you were held in the hospital until you got better, against your will. In this burgeoning field of gynecology, tools to help assess vaginal or cervical health were needed and so they were developed. For instance, the duckbill speculum which is a very close if not the exact thing that we use today. That was developed by James Marion Sims who was the so-called father of modern gynecology and also one of the most unethical people I have read about while working on the podcast.
Erin Allmann Updyke	Not surprised about that.
Erin Welsh	Oh no. He operated almost exclusively on enslaved black women and never with anesthesia and conducted all sorts of medicalized torture as well as perpetuated a lot of misinformation. Please read the book 'Medical Bondage' by Deirdre Cooper Owens for more info about him. It's so good. Okay, anyway, back to cervical cancer. So what these new and improved speculums did was allow doctors to visualize these different lesions and record their observations so that ultimately the link between cervical lesions or cauliflower growths and later developing advanced cancer of the womb was made. And this visibility or observability of two of the most common cancers to affect women, so like breast cancer and cervical cancer, led to cancers overall being seen as a quote "female ailment", usually attributed to some part of the woman's reproductive tract. So like hysteria, right, like it must be from an overactive uterus.
Erin Allmann Updyke	Right.
Erin Welsh	As if anyone knew what that meant.
Erin Allmann Updyke	Yeah a wandering uterus.
Erin Welsh	A wandering uterus. And then second book recommendation here, 'Illness is a Metaphor' by Susan Sontag. Okay. So once doctors had made the link between these lesions and cancer, they started to try to treat these ulcers to prevent their spread. Again cauterization or treatment with corrosive chemicals or simply removal of the affected areas, so like full-on trying to remove a cervix or uterus. These were pretty much the options that they chose. And in these days these more drastic options were nearly almost always fatal. And in the days before anesthesia, unbelievably excruciating. Even after surgical practices and diagnostic tools improved, focus turned towards ways to detect cancers early and prevent them from spreading. Enter the pap smear. The pap smear was developed by none other than Dr. George Papanicolaou in the 1920s.
Erin Allmann Updyke	The 1920s!
Erin Welsh	Yeah.
Erin Allmann Updyke	I didn't realize it was that long ago.

Erin Welsh	Yeah. So he had started work on mice to develop a lab test to show how changing levels of estrogen could be detected in changes in the vaginal lining and he was like, 'Well I really wanna translate this research into humans, I could use it to stimulate menstruation or treat infertility.' But then he was like, 'I actually have no idea what a normal vaginal smear looks like. Like what's the baseline?' And so once he started looking for that baseline he began observing that some of the smears had irregular-looking cells and subsequent gynecological examination revealed that they had early cancer of the cervix. And his article that described this finding didn't really gain a lot of traction and many doctors remained skeptical for a number of years. But over time this use for vaginal smears grew and they were then named the Papanicolaou or pap smear in his honor, Dr. George Pap.
Erin Allmann Updyke	Pap!
Erin Welsh	The pap smear, especially the simplified version of the test which was developed by Dr. Anna Marion Hilliard in the 50s I think, did a lot to advance knowledge in terms of what proportion of lesions were likely to remain localized and which were likely to advance to invasive malignancies. And the 1960s and 70s continued with this trend of early detection and lesion removal with fewer and fewer hysterectomies performed, instead being replaced by less invasive surgical procedures. And so this was a great improvement from the early days of cervical cancer. Early detection methods had been developed and physicians realized that precancerous lesions were pretty fragile, meaning that their removal often meant that the cancer itself was gone. But issues remained.
	These cervical biopsies which were described as minor surgical procedures not only still had and have risks associated with them, but they could also be very painful and associated with uncomfortable side effects. And a positive diagnosis itself could be quite terrifying since it usually meant additional diagnostic tests which can be distressing especially because there often wasn't adequate communication, and that problem lingers today, about what exactly the tests are for or what the finding is. The consensus of course, and I know you'll talk more about this, is that regular screening helps detect and effectively treat cervical cancers but that in many places clear guidelines didn't exist or were being developed at a slow pace for how frequently someone should be tested, or the age group that should be tested.
Erin Allmann Updyke	I could get literally so excited talking about guidelines.
Erin Welsh	Oh yes. And I think that often one of the biggest problems is just like once again, we always come back to this, communication. Right, so like not just in public health campaigns, which those were pushed really hard in the 60s and 70s but also between physician and patient.
Erin Allmann Updyke	Right.
Erin Welsh	Open communication, clear communication, ask as many questions as you want, I will be as direct and informative as possible, whatever. So anyway. But the bottom line is that for the most part, effective treatment is no substitute for complete prevention.
Erin Allmann Updyke	Yeah.
Erin Welsh	And the only way to do that was to understand what caused these cancers. This was not a new question. Even before cancer, like the Big C cancer was defined medically or cellularly, people had wondered about the causes of various cancers including cervical cancer. And there was quite a long list in the case of cervical cancer of suspected causes: masturbation, excessive sexual activity, sexual abstinence, sterility, syphilis and other STIs, great sadness, dangers of-
Erin Allmann Updyke	Great sadness? Oh my gosh.

Erin Welsh	(laughs) Great sadness. Dangers of urban life, fright, childbirth, abortion, and menopause. Literally anything.
Erin Allmann Updyke	Anything. (laughs)
Erin Welsh	Yeah.
Erin Allmann Updyke	Anything that happens near the cervix.
Erin Welsh	Yep. Then the field of medical or health statistics finally shed some light on the issue in the mid 1800s when Italian surgeon Domenico Rigoni-Stern published his finding that nuns had a much lower rate of uterine cancer and a higher rate of breast cancer than married women. And this did not distinguish between like-
Erin Allmann Updyke	Like true uterine vs cervical.
Erin Welsh	Right, versus true uterine. This research not only hinted at a potential sexual link to cervical cancer but it also suggested that different cancers might have different causes, which is-
Erin Allmann Updyke	Ooh.
Erin Welsh	That's like a pretty big-
Erin Allmann Updyke	That's a huge...
Erin Welsh	Yeah.
Erin Allmann Updyke	That's in the 1800s?
Erin Welsh	Yeah.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. Other research from around the same time supported the sexual link. In 120 cases of uterine cancer, 5.83% were from single women, 86.6% were married, and 7.5% were widows. Later when cervical cancer was distinguished from cancer of the uterine body, the link between sex and cervical cancer remained and additional evidence, like how cervical cancer was lower in groups that practiced male circumcision and how sexually active but unmarried women experience similar rates of cervical cancer as married women, these things further supported this link. It seemed so clear that cervical cancer was tied to sexual activity that by the 1970s there were articles in scientific journals asking if cervical cancer was a sexually transmitted infection. I mean and it certainly seemed to be. But which one?
Erin Allmann Updyke	Which one?
Erin Welsh	Was it syphilis? Trichomonas?
Erin Allmann Updyke	Was it gonorrhea?
Erin Welsh	Or how about the great boogeyman of the sexual revolution? Herpes simplex 2.

Erin Allmann Updyke	Herpes! Must've been herp.
Erin Welsh	Must've been herp. And this last one, HSV-2 - I was HPV, HSV, yeah.
Erin Allmann Updyke	(laughs)
Erin Welsh	This last one, Herpes simplex virus 2, this emerged as the favorite partially because it did have some support from epidemiological studies. But at least one researcher wasn't so sure. Dr. Harald zur Hausen, who is a German virologist, could not find Herpes simplex virus 2 reliably in the many cervical cancer biopsies he screened and so he came to the conclusion that it wasn't the cause and he presented his findings at the 1972 - get a load of this name - International Conference on Herpes Virus and Cervical Cancer.
Erin Allmann Updyke	What?
Erin Welsh	It was very pretty much accepted.
Erin Allmann Updyke	Wow.
Erin Welsh	Like there was a whole conference about it. So when he presented his findings he was met with, quote "stony silence", which he later found to be, quote "the low point of his career." Which is really depressing.
Erin Allmann Updyke	Aw, poor guy.
Erin Welsh	But he wasn't discouraged and he continued his work on HPV which he thought was a much better candidate for cervical cancer than herpes.
Erin Allmann Updyke	So that was the low point cause things went up from there.
Erin Welsh	Things went way up. He published his hypothesis in 1976 and that was a year before his lab group discovered that yes, there were actually multiple types of HPV. And the final breakthrough came in 1982 when his research fellow Mathias Durst isolated a new HPV type, HPV 16 from a cervical cancer biopsy.
Erin Allmann Updyke	(gasps) Ooh!
Erin Welsh	He came up with the naming system by the way, or like the numbering system.
Erin Allmann Updyke	Oh, okay.
Erin Welsh	HPV 18, another cancer-causing type, was found shortly after and nearly all of the lab specimens of cervical cancer biopsies contained one of these viruses. And to zur Hausen the link was clear as was the path forward. In 1984 he approached pharmaceutical companies to start working on a vaccine but they all turned him down saying, 'Yeah, that's not gonna be profitable, there are more urgent problems to solve.' I know. And the scientific community was like almost as dismissive of his findings for the most part. Like it wasn't really until the mid 90s and after extensive epidemiological work that there was wide consensus on HPV's role in cervical cancer. And the landmark study that erased all doubt was published in 1995 and involved over a thousand cervical tumors from 22 countries and it showed that 99.7% of the tumors were HPV positive. So then 11 years after this study in 2006, the HPV vaccine Gardasil, the first HPV vaccine, was approved by the FDA to considerable controversy.

Erin Allmann Updyke	Oh yeah.
Erin Welsh	Which I think you'll go into.
Erin Allmann Updyke	Yeah.
Erin Welsh	And since then many other countries have approved its use and incorporated it into recommended vaccination programs to varying degrees of effectiveness and also with some very interesting messaging. I also wanna note real quick that zur Hausen was awarded a Nobel Prize I believe in 2008 for making this link.
Erin Allmann Updyke	I'm sorry, I just wanna go back to the fact that this link wasn't cemented in scientific consensus until the mid 90s.
Erin Welsh	Mm-hmm. That was sort of like the final, like I think that there had been steady growth of acceptance of this.
Erin Allmann Updyke	Yeah. Oh my.
Erin Welsh	It's an interesting timeline, that.
Erin Allmann Updyke	It's fascinating, that timeline, Erin.
Erin Welsh	So Erin.
Erin Allmann Updyke	Oh!
Erin Welsh	I'm hoping you're about to tell me more about some of these vaccine controversies, in particular how the vaccine was targeted to certain groups or certain people and how much of an impact we can see now 15 years after it was first introduced.
Erin Allmann Updyke	I can't wait. We'll get into it right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	I wanna get into all of that juicy vaccine info and cervical cancers statistics and everything and also just like a lot a Erin and Erin's hot takes, how about that?
Erin Welsh	(laughs)
Erin Allmann Updyke	But first let's bring it all the way back to HPV for a minute cause I really wanna stress just how prevalent this virus is. And this is specifically for genital HPV, so we're not even gonna account for the fact that every child probably has a wart and a lot of adults do too at some point on their skin. When we're talking about genital HPV, point prevalence, so overall if you just at any given time took a sample of random adults, anywhere from 3-45% of them would be positive for HPV, even without any symptoms.
Erin Welsh	I mean that's a very high percentage.

Erin Allmann Updyke	And that's just point prevalence. If you look at lifetime risk, which means because most people who get this infection will clear it, so they might have had it but when you sample them they come up negative, so if you look at lifetime risk we're talking 80% of people are likely to be infected with HPV at some point in their lives.
Erin Welsh	It's almost an inevitability.
Erin Allmann Updyke	It's almost an inevitability. But that's just HPV. Let's now focus on cervical cancer because we have the most data for cervical cancer. So worldwide today, well 2018 data, cervical cancer causes an estimated 570,000 new cases every year, with-
Erin Welsh	570,000?!
Erin Allmann Updyke	570,000 new cases and over 311,000 deaths due to cervical cancer.
Erin Welsh	Every year.
Erin Allmann Updyke	Every year. HPV worldwide is the 4th leading cause of cancer in people with a cervix. The 4th leading cause of cancer in people with a cervix worldwide.
Erin Welsh	It's so interesting to me the lack of visibility between something like breast cancer, lung cancer, and then cervical cancer.
Erin Allmann Updyke	Mm-hmm, mm-hmm. Well here's part of it. The vast majority of these new cases and deaths that are due to cervical cancer are in low and middle income countries where access to screenings and vaccines is very limited if it's even existent at all. If we look briefly at data in the U.S. there is an estimated 36,000 new cases of HPV-associated cancers every year, that's all HPV-associated cancers.
Erin Welsh	Okay.
Erin Allmann Updyke	So in the U.S. that includes about 14,000 cases of oropharyngeal or throat cancer, 11,000 cases of cervical cancer, 6000 cases of anal cancer, and over 3000 cases of vaginal or vulvar cancer. And 1000 cases of penile cancer!
Erin Welsh	Dang.
Erin Allmann Updyke	That's a lot of humans.
Erin Welsh	That's a lot of humans.
Erin Allmann Updyke	Worldwide and I do kind of want to focus on this for a second because it's so underrepresented, like talk about cervical cancer being underrepresented, 85% of anal cancers are associated with HPV. 85%. 46% of penile cancers, HPV. Anywhere from 33-72% of oropharyngeal, HPV. It's a lot of cancers.
Erin Welsh	Yeah.
Erin Allmann Updyke	And while we have screening programs in a lot of places that can detect cervical cancer which is incredible because it's very effective, the pap smear is a screening tool that can detect precancerous changes that can then be treated so that it never becomes cancer.

Erin Welsh	If we had something equivalent to a pap smear for like other kinds of cancers, it would be incredible.
Erin Allmann Updyke	Absolutely incredible.
Erin Welsh	It's hard to wrap your brain around just how amazing it is to be able to be like there is cancer developing or precancer developing, we can do something about it.
Erin Allmann Updyke	The other thing too is that the way that you can then treat those precancerous changes that you might detect on a pap smear is also not nearly as invasive as the way that you would need to treat precancerous changes if you could even detect those other places. So not only are we able to detect pre-cancer before it becomes cancer but we can then also treat it before it becomes cancer. It's really similar to the way that we can do colon cancer screenings, that's really the only other one that we can do in the same way where if we see a polyp, we can remove it and we treated your cancer before it became cancer.
Erin Welsh	Gotcha, yeah.
Erin Allmann Updyke	Okay. And that's incredible. But it isn't perfect. Pap smears are an invasive test, they're uncomfortable, a lot of people might not be comfortable even getting them even in places where they are easily accessible. They're also both operator and reader dependent and so it requires a lot of infrastructure that in low and middle income countries just might not exist at all. And in some cases because they are so dependent on the reader and the operator, they can be over-read and then potentially lead to unnecessary procedures that do have risks associated with them.
Erin Welsh	Right.
Erin Allmann Updyke	So they are not a perfect thing. But on top of that, they are specific to cervical cancer and HPV causes a lot more than just cervical cancer. So the fact that we have a vaccine is beyond incredible.
Erin Welsh	Yeah.
Erin Allmann Updyke	Because this is a vaccine that can prevent all of these types of cancer. Not 100% of all of these types of cancer, but 100% of cervical cancers and a lot of the proportion of all of these other cancers. So the question is why do we even still have cervical cancer 15 years out from this vaccine?
Erin Welsh	Well, a lot of different answers there.
Erin Allmann Updyke	It's a lot of different answers. Like you said Erin, a lot of it in certain countries like the U.S. has to do with how this vaccine was marketed at the beginning. In most places where it was rolled out, it was only recommended for people with a cervix except it was marketed as 'give this STI prevention vaccine to your young girls'.
Erin Welsh	Mm-hmm, mm-hmm.
Erin Allmann Updyke	And so that was interpreted by a lot of people as a vaccine to promote sexual promiscuity, which we all know is not allowed in our culture.

Erin Welsh	And also that's not what this vaccine does.
Erin Allmann Updyke	Not in the slightest but that is absolutely how it was perceived.
Erin Welsh	Yeah.
Erin Allmann Updyke	So the marketing failures were really immense, but on top of that, this was a very expensive vaccine especially when it first came out.
Erin Welsh	Holy cow, yeah.
Erin Allmann Updyke	It was $120 a dose, which compared to most childhood vaccines is immense. You can imagine that in low and middle income countries, that is absolutely an unattainable cost. Even for most people in the U.S., $120 a dose for a vaccine that needs 2-3 doses, that's a lot of money.
Erin Welsh	And is it $120 a dose in other countries as well or is it just the U.S. has artificially inflated the price because that's just what the U.S. does?
Erin Allmann Updyke	So I couldn't get a great answer to that, it varies a lot but today because of a lot of different institutes that help subsidize the funding, it can be available in a lot of countries as low as, in theory, 20 cents or $4.50 a dose. Since 2008, which is just two years after it was introduced, PAHO which is the Pan American Health Organization has been subsidizing HPV vaccines at $8.50 per dose. So Latin America and the Caribbean actually have the proportion of countries that have national programs if you look at all the different regions.
Erin Welsh	That's cool.
Erin Allmann Updyke	But overall not a very impressive percentage of countries have instituted national HPV vaccine campaigns. As of late 2017, only about 40% of countries had instituted national HPV vaccine programs. And you can imagine that the percentage varies greatly based on income. So 77% of high income countries have vaccination programs but only 7% of low income countries have vaccination programs. So this vaccine is not being evenly distributed across the globe which is why we still have cervical cancer deaths happening every day across the globe.
Erin Welsh	It's is so frustrating.
Erin Allmann Updyke	It really is. The World Health Organization has a lot of different goals to try and address this, their current goals are to vaccinate 90% of people with a cervix by age 15 and screen 70% of people with a cervix at least twice between the ages of 35-45 because again, screening is still really important. But we are nowhere near those goals.
Erin Welsh	And I understand that you have to have reasonable goals or at least like benchmarks, but why is it still just people with a cervix? Why is it not everyone when everyone can become infected, everyone can develop some kind of cancer, and everyone can transmit it to somebody else.
Erin Allmann Updyke	(singing) Erin sing it!
Erin Welsh	(laughs)

Erin Allmann Updyke	That's like the biggest... Okay, I get so intense when I think about that and I honestly, because in the U.S. now finally the recommendation is everyone. All adolescents should be vaccinated starting at age 11/12, it can be as early as 9. I have big issue with the fact that the U.S. still doesn't make this a mandatory vaccine for school entry. It's absolutely absurd in my, Erin's, personal opinion. Because DTaP is required, meningitis is required, Hepatitis B is required and that's not roaming around schools so like, come on. But anyways. Globally you're right, the recommendation still isn't for everyone to get this vaccine even though we know that not only can people with a cervix get HPV from people without a cervix, so if you're not vaccinating everyone then you just have a bunch of people that are harboring HPV to then be spread to everyone else. But also yeah, then we're not preventing penile cancer or anal cancer in people without a cervix, or oropharyngeal cancer. Like this is a lot bigger than just cervical cancer, this is a vaccine that can prevent a lot of different types of cancer. Everyone deserves access to it.
Erin Welsh	They do. It's endlessly frustrating.
Erin Allmann Updyke	It's endlessly frustrating.
Erin Welsh	My big question is part of the controversy around the HPV vaccine when it first was released was that, well we don't know whether it's going to prevent cancer, we just-
Erin Allmann Updyke	Oh yeah, Erin!
Erin Welsh	Right, so now it's been 15 years we should've seen the effects, right? In the generation, the first cohort that was vaccinated.
Erin Allmann Updyke	Yes.
Erin Welsh	Well first of all I have a question about the average age of onset for cervical cancer.
Erin Allmann Updyke	Oh it's 59 is the average age of death due to cervical cancer.
Erin Welsh	Okay.
Erin Allmann Updyke	Yep.
Erin Welsh	But it could happen earlier.
Erin Allmann Updyke	Absolutely and it's one of the most common causes of cancer in people with a cervix under age 40. So it can definitely happen in younger people as well.
Erin Welsh	Okay.
Erin Allmann Updyke	Because this is a sexually transmitted infection that has kind of highest incidence at younger ages but usually takes 10-20 years to then cause cancer.
Erin Welsh	Okay.
Erin Allmann Updyke	And then younger people are also more likely to clear the infection so it's kind of, yeah.
Erin Welsh	Another question about the vaccine's durability. How long are you protected?

Erin Allmann Updyke	Well that's a very good question. We know for sure at least 8 years, it's likely even longer than that.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. It's likely pretty long-term and there's some cross-protection as well. So even though the sort of broadest vaccine that we have covers nine subtypes, there's thought to be at least some cross-protection to protect you against further types as well, if that makes sense.
Erin Welsh	Gotcha.
Erin Allmann Updyke	But you have full protection against either 2, 4, or 9 subtypes depending on which vaccine you get. But you asked, Erin, do we have any data to say this actually prevents cervical cancer? Cause you're right, when this vaccine first came out everyone was like, 'Well, it protects against HPV infection and maybe like precancer but we can't say for sure that it protects against cancer.'
Erin Welsh	(laughs)
Erin Allmann Updyke	Like give me strength.
Erin Welsh	I know, I know.
Erin Allmann Updyke	It does. The answer that we have now is without a doubt it absolutely does. If you'd like some hard data on it, there's a beautiful study out of Sweden where they implemented a school-based vaccination program and studied over a million people with a cervix, about half of whom received the vaccine and over the time period studied, only 19 people who had received at least one does of the vaccine were diagnosed with cervical cancer while over 500 who hadn't were diagnosed with cervical cancer.
Erin Welsh	That's pretty clear.
Erin Allmann Updyke	What's even more clear is that the protective effects were far stronger for people who were vaccinated before age 17. So the earlier that people get the vaccine, the better it works. Not only because it seems to work better in younger people but you have to get this vaccine before you are exposed to HPV. HPV is a sexually transmitted disease which means you need to get the vaccine before you ever have sexual activity for it to be the most effective.
Erin Welsh	And so you mean any HPV or you mean just the sexually transmitted HPVs?
Erin Allmann Updyke	Sexually transmitted HPVs.
Erin Welsh	Yeah, okay.
Erin Allmann Updyke	Yeah. So that's why the recommended age is 11-12 or even as young as 9 because the idea is to give it to people who have not yet engaged in sexual activity, like well before so that you're really preventing this. Now that doesn't mean that you can't get it if you have already had sexual activity or if you're over age 12, it's recommended as like a catch-up up to age 26 and now it's approved all the way up to age 40. So that's HPV, guys. And cervical cancer.

Erin Welsh	It's so interesting. This is a big one.
Erin Allmann Updyke	Oh my gosh it's way bigger than I thought, I feel like I talked for seven years.
Erin Welsh	There's a lot to talk about.
Erin Allmann Updyke	I mean, I'm sure that I missed a lot of things also so why don't we talk about our sources so that people can do a lot more reading and learn all the things that we probably forgot.
Erin Welsh	Sounds great. So I will shoutout just a couple of things. One is a book called 'A Woman's Disease: The History of Cervical Cancer' by Ilana Lowy. Then also a paper by Onon et al 'History of human papillomaviruses, warts, and cancer'. By Van Doorslaer 2013, 'Evolution of the papillomaviridae'. And finally a great paper by Burns 1992, 'Warts and all: the history and folklore of warts'.
Erin Allmann Updyke	I love it. (laughs) I have a lot of different papers ranging form everything from a lot more detail on the pathophysiology and natural history of HPV infection and the specific mechanisms on how it causes cancer all the way up to the global distribution and the effects of the vaccine and all of that kind of stuff. You can find a list of our sources from this episode and every single one of our episodes on our website thispodcastwillkillyou.com under the EPISODES tab.
Erin Welsh	Thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	Thank you to Exactly Right network of whom we are very proud to be a member.
Erin Welsh	And thank you to you listeners, for listening. And for suggesting this episode so many times, we're so excited to finally give it to you and hopefully you like it.
Erin Allmann Updyke	Yeah. I learned a lot about the history of HPV and cervical cancer, which is exciting.
Erin Welsh	Yeah. I learned a lot about the biology and the current events. (laughs)
Erin Allmann Updyke	(laughs) My gosh.
Erin Welsh	Wow.
Erin Allmann Updyke	How about that.
Erin Welsh	Well, until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.