

**About Health TV with Jeanne Blake**  
**Cervical Cancer**  
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JEANNE BLAKE: Welcome to *About Health TV*. I'm Jeanne Blake. Every year in this country 13,000 women develop cervical cancer. One-third of them die from the disease. On this edition of *About Health TV* we'll talk about cervical cancer and a new vaccine that may prevent it. I'm joined for the discussion about this by Dr. Christopher Crum, who is the director of women's and perinatal pathology at Boston's Brigham and Women's Hospital. Doctor, thank you for coming in. Almost all cases of cervical cancer are caused by a virus?

DR. CRUM: That's correct. It's the papilloma virus, which is a sexually transmitted infection that most women acquire during the reproductive years.

JEANNE BLAKE: What happens in the cervix that this results in cancer in some women?

DR. CRUM: Well, the cervix is uniquely receptive, or you might say vulnerable to papilloma virus infection. Women do get papilloma virus infections on the external genitalia, which are called genital warts. I think they're very familiar with that. But cervical infections occur probably because the virus targets the cells that are in the cervix and they're uniquely receptive to the virus, and, therefore, the consequences of this infection, which are the abnormal Pap smear, the abnormal cells that we see in the cervix in young women, are quite common. Probably the vast majority of young women will be exposed to these viruses during their sexually active years, particularly their younger years.

JEANNE BLAKE: But not every woman who gets papilloma virus will develop cervical cancer. What percentage will?

DR. CRUM: Well, that is correct. Only about perhaps 5% or 10% of women who are exposed actually develop what you might call a precancerous change, and out of perhaps 100 women only one, or at the most perhaps on average one and a half, would actually develop cervical cancer in their lifetime.

JEANNE BLAKE: But if someone does get the diagnosis of cervical cancer, they basically know that it was by exposure through unprotected sexual intercourse to HPV?

DR. CRUM: Well, certainly the vast majority of cervical cancers can be linked to papilloma viruses, and most of them will have been obtained by the sexual transmission. That's correct.

JEANNE BLAKE: I decided, in preparing this program, to talk with young women in particular about their knowledge about the link between cervical cancer and HPV. Let's listen to what they said.

[VIDEO CLIP]

JEANNE BLAKE: When you think of unprotected sexual intercourse, what are the health risks and/or the diseases that you associate with that?

RESPONDENT 1: The diseases? Like everything. AIDS.

RESPONDENT 2: AIDS, the HIV.

RESPONDENT 1: Chlamydia, gonorrhea.

RESPONDENT 3: Transmitted diseases.

RESPONDENT 4: Gonorrhea, chlamydia.

JEANNE BLAKE: Do you think, when you think about those diseases, do you think about cervical cancer being caused by unprotected sex?

RESPONDENT 1: It's not the first thing you think of. I know it's connected to it, but ...

RESPONDENT 2: It's not the first thing that pops into my mind, more of the STDs, not the cervical cancer thing.

RESPONDENT 3: I think that women who are sexually active know about STDs and they know about cancers that are specific to women separately, but that they don't necessarily make the connection between the two.

JEANNE BLAKE: And why do you think that is?

RESPONDENT 3: For whatever reason, there's just not that much awareness and probably not enough education on the issue.

JEANNE BLAKE: You knew about it, Kaitlin, that there was a link. How did you know?

KAITLIN: The only reason I knew is because I just took a special class on it at school, and that's the only way. I mean, my parents have never talked to me about it, and it's something that people in our society tend to shy away from, talking about sex and STDs, I think.

JEANNE BLAKE: So I'm assuming that you would advocate that young men and women are taught about this at an earlier age?

KAITLIN: Definitely. I think it's a really important issue that people should know about.

[END CLIP]

JEANNE BLAKE: I'll bet it doesn't surprise you that women that I talked with would mention HIV and chlamydia but not cervical cancer.

DR. CRUM: I think that's probably to be expected. Most young women nowadays, I think, are being taught that the principal concerns, I think, about unprotected sex are pregnancy and HIV. And most of the ones I've talked to in the clinic and most practices in the past have been pretty cognizant of gonorrhea and chlamydia and even herpes. But very few of them have been very clear on HPV, and in talking to my own daughters about it they informed me that in high school health classes that was one topic that really wasn't discussed, although they discussed all the other sexually transmitted diseases.

JEANNE BLAKE: But why do you think that is?

DR. CRUM: It's a good question. I think that probably this lag phase between actual exposure to HPV and the development of cancer is such a broad space of time that it really isn't seen as a major concern for young women in their teens. And I think, to be practical, it probably isn't.

JEANNE BLAKE: Well, I mean, then smoking cigarettes for teens isn't so dangerous because there's a lag time between smoking and lung cancer.

DR. CRUM: Absolutely. And I think that's why education about cervical cancer is important. I expect that some of this has been handled by the fact that most women, once they become sexually active, either know or are told by their physicians that they should get a Pap smear. And presumably the Pap smear is the protecting procedure that we use to prevent cervical cancer.

JEANNE BLAKE: And that's because, if found in its early stages, where there are going to be cells that are changing, it's very curable.

DR. CRUM: That is correct. If you take a group of young women between 15 and 25, very few of them are going to be found to have cancer on their first examination. It's extremely uncommon. But clearly they may be infected. They may have an abnormal Pap smear. That is really what's looked for. It doesn't mean they aren't anxious when they get that diagnosis of an abnormal Pap smear, but clearly at that age it's detected at a very early point where it might actually go away on its own.

JEANNE BLAKE: And how does that happen? I mean, I do know that it does. I do know that women who have abnormal cells can go back six months later and it's corrected itself. What happens in that? How does that work?

DR. CRUM: Well, no one really knows for sure, but only a small number of women ever actually get cancer who get infected, as we discussed previously. You might see a scenario where a woman has sexual intercourse, she acquires the virus. The virus may linger in the genital tract for six months or so, or 12 months, and then produce perhaps an abnormality that can be seen through the microscope in the Pap smear. However, many of those women may have a regression or a disappearance before that happens. Even those who develop an abnormality, it may go away.

JEANNE BLAKE: So it's not like herpes that stays there forever.

DR. CRUM: That's correct. Herpes is basically programmed once it gets inside the body to stay there. Fortunately, for most women it doesn't make much trouble while it's there except for occasional reinfections. I'm sure there are some women that would argue that point. But in the case of the HPV, the host immune system is actually very efficient at getting rid of most infections. It's just that one small group of infections that might produce a persisting precancerous change that might progress to cancer. And the Pap smear is designed to pick that up, hopefully, before it reaches the cancerous stage.

JEANNE BLAKE: I guess this is the chance, before we talk about the vaccine, to give a plug for Pap smears, because you've just made it so clear that if this is a disease that is so preventable because of an early change in cells, it's a shame that women aren't getting the Pap smears in the numbers that they need to.

DR. CRUM: Well, fortunately it's much better than it used to be, but clearly even as vaccines come on the horizon I think the Pap smear is going to be an important staple in cancer prevention for some time to come.

JEANNE BLAKE: How come? I mean, that confuses me about my next question, which was going to be why do we need a vaccine if we have a Pap smear and it's so effective?

DR. CRUM: I think if you have a vaccine, what you will do is make a major impact on a couple of things in this country. Number one is that if you had a vaccine, for example, that would, let's say, address many of the papilloma viruses that are associated with cancer, or several of them even, you would see probably an immediate drop in abnormal Pap smears in those patients who were vaccinated. That may not have a whole lot to do about preventing cancer so much, but it has a great deal to do with the costs of Pap smear management. In addition, there is still a reasonable number of women in this country who do develop cancer. Some of them have been screened by Pap smears and somehow the system didn't serve them, and some of them didn't get Pap smears at all. So if you were to reach those patients with a vaccine, you can imagine you would also reduce further the cancer risks. Now, if you go over to some other country, for example, where there is no Pap smears available, you can imagine the impact of a vaccine. But in this country, given the attention to cancer prevention, you're going to have a Pap smear for some time even with a successful vaccine, because no one is going to be absolutely certain the vaccine is effective until you've gone out several years, and it will be two or three decades. So I expect the Pap smear or some kind of screening program designed to pick up those uncovered patients or missed cases will still be in effect for some time.

JEANNE BLAKE: I think it's worth noting ... you mentioned worldwide ... I mean there are 450,000 cases of cervical cancer worldwide, so we're not talking about a vaccination for this very, very small number of cancers.

DR. CRUM: That is correct. We're very privileged in this country by a very comprehensive Pap smear program and a considerable amount of economic resources that are devoted to preventing cervical cancer. Other countries may be very lucky to get a single Pap smear for each women in their

lifetime.

JEANNE BLAKE: So let's talk about the vaccine. How does it work? It's not yet available. It's been studied and it's been shown to be highly effective. So tell us what we do know about it.

DR. CRUM: Well, the vaccine was developed about 12 years ago, and really the major development was the ability to actually produce an artificial virus, if you will, in the laboratory.

JEANNE BLAKE: I don't want to confuse folks. It was developed 12 years ago, so why is it in the news today?

DR. CRUM: It's in the news today because once it was developed it took 12 years to actually come to a point where we could see its effect on humans and its beneficial effect. It was discovered, and then it had to be manufactured in large quantities by one company, which was Merck, but there are others as well. And once they succeeded in producing sufficient vaccine material, then they went on and recruited young women. They went to many student health programs around the country. Many of my colleagues who I know were involved in these studies and many universities. They then recruited these young women. My daughter knows one who said, Yes, I was in that particular study. It was very exciting for them when they saw the results. But these young women then came in and they were vaccinated. They were not told to change their lifestyle, and they were called at intervals to see whether or not they became infected by HPV. Now, in this case they only used one virus. They used HPV type 16.

JEANNE BLAKE: And how many are there?

DR. CRUM: Well, there probably are 20 or more viruses that might have been associated with cancer, but four or five of them probably make up 85% of the causes of cancer. And so HPV-16 is present in at least half of cancers, so we decided to pick the prototypical cancer-causing virus to target. And what they did was, once they vaccinated these young women – and they did it in three different stages, simply a vaccine in the arm like you would for any vaccine, and they then followed them at intervals to see if they became infected by sampling their cervix secretions, looking for HPV type 16, and then when they developed an abnormality in their Pap smear and then, let's say, got a biopsy and looked at the tissue to determine if that tissue contained HPV-16.

JEANNE BLAKE: Okay?

DR. CRUM: And it turned out those young women had very rarely developed HPV-16 infections if they could be kept by just molecular means. This is notwithstanding the abnormalities. They actually had the same percentage of abnormalities in both the treated and untreated group. But in the treated group, none of the abnormalities were associated with type 16.

JEANNE BLAKE: So that's a grand slam? I mean, that's huge.

DR. CRUM: Well, no one is going to follow a group of women and watch them get cancer. You certainly wouldn't do that. But certainly the fact that they did not develop a precancer associated with that virus is pretty powerful evidence that they would probably not develop the cancer either.

JEANNE BLAKE: Now my question is, if there are five strains the vaccination is targeting ... hoped and thought to prevent half those cancers, is there a risk that women who get the vaccination will then feel somehow this sense of security and allow themselves to be exposed? Are there HPV, human HPV, by having unprotected sex?

DR. CRUM: Well, it's an interesting question. I think that probably when these vaccines come around they're probably not going to be taking women in their teens or 20s and vaccinating them and giving them that option to consider that. I expect they're going to be vaccinating young people perhaps in their childhood. It might become one of many of the vaccines that are given then, and by the time they become teenagers they're going to be told what is the most appropriate way to prevent cancer. At that point, it may be some other type of test where it may be a Pap smear at a given interval, but I expect that we're not going to be vaccinating people at a time when they may misinterpret its significance. Hopefully it will cover enough ... the vaccines that will be developed will cover enough viral types to protect 80% to 85% eventually.

JEANNE BLAKE: Now, I keep talking about women, and I only interviewed women, and I'm surprised you didn't criticize me for that. I'm glad nobody has picked up on that.

DR. CRUM: I have a wife and two daughters, so I've been interviewed pretty frequently about that.

JEANNE BLAKE: But the point is, women don't just have HPV fall out of the sky. It's transmitted between men and women. So my question is, will men be vaccinated?

DR. CRUM: Well, you can certainly argue to vaccinate men if only to protect women. I think there is some argument to increase the number of individuals in the population that have been vaccinated ...

JEANNE BLAKE: Well, so if men contract HPV, is there any manifestation in them physically or do they just pass it on?

DR. CRUM: In general, the manifestations are not obvious. There have been very detailed studies looking at the penis of men, using even colposcopes, which are the same machines we use to look at women, using magnification type of apparatus to look at the small precancers on the penis. And men do get small abnormalities, but they're basically asymptomatic. Some men do get genital warts and some get rather pronounced infections, but most men ... most women who are watching this and who say yes, I have an abnormal Pap smear, I have HPV infection, their boyfriends are not going to have any obvious abnormality in their genital area. So yes, it is more or less transmitted without the male knowing that he is infected. That is correct.

JEANNE BLAKE: Doctor, you started to describe some very key steps that took place 12 years ago that allowed us to have this vaccination at the place it is now, really developing a fake virus. Help us understand how that happened and how the vaccine works and why that was so important and necessary.

DR. CRUM: Well, this was actually a discovery made by E.M. Frazier and his colleagues in Australia back around 1990. Several groups in this country have also done it, such as the group at the National Cancer Institute and other institutions such as Georgetown and others. And this was basically a technique by which one could manufacture these ... they were called viral-like particles. They looked like the outer surface of the virus, but they don't contain any infectious virus. And so it's the ideal vaccine, in that you can actually give the virus without causing infection. In papilloma virus that was a specifically difficult problem, because during the 1980s, although we knew much about the virus, we were not able to manufacture it. So once these individuals began to manufacture this in the laboratory, it then, as I mentioned, went on to be used as a vaccine. The effective aspect of this vaccine was that once it was administered it would generate an immune response by the host, if you will ...

JEANNE BLAKE: The host being the body.

DR. CRUM: By the body that would recognize any virus that came into the genital tract.

JEANNE BLAKE: Basically the body thinks that that is the virus.

DR. CRUM: That is correct. They think it's been exposed to this virus so it develops an immune response, and so any virus that comes afterwards is facing an immune system that's awaiting it, if you will, or ready for it. And clearly the fact that viruses disappear over time. For example, in natural infection, you find a lot of it in young women and very little in older women. And so there is clearly evidence that the human can produce an effective immune response even to natural infection. But what this vaccine does is, it basically preempts that infection by preparing the body for the virus in advance. And that's why it's so effective.

JEANNE BLAKE: But it won't work in women that already have a precancerous condition.

DR. CRUM: No, I don't think so. I think most of the studies even conducted by these investigators have shown that. Both animal studies and animal systems and some preliminary human studies suggest that this is not the case and that you can vaccinate someone ahead of time. It is possible you might vaccinate them right as they're being exposed and have some success, but once they develop a precancer or a cancer, they will not have success in rejecting it with this vaccine. There are other types of vaccines being tested, or let's say therapeutics, which do employ a vaccination-type strategy, but they are looking at different components of the virus as methods for perhaps getting or inducing precancers or cancers to regress. They are much more in the development stage and don't, at this point, hold the promise that this vaccine does.

JEANNE BLAKE: Even though you said that probably if the vaccine were available today it would be targeted to younger people, I did ask some women whether they would consider getting the vaccination if it were available. Let's listen to what they had to say.

[VIDEO CLIP]

RESPONDENT 1: I wouldn't necessarily be putting myself in a situation that would be that high risk, so no, probably not.

RESPONDENT 2: I definitely would. I wouldn't put myself in a situation where I was having unprotected sex; at least I can't say that I would. But just as a precautionary measure, I would definitely get the vaccination, because you never know. Certain circumstances arise.

JEANNE BLAKE: Such as?

RESPONDENT 2: Such as possibly getting sexually assaulted or raped, which women have to worry about in today's society, unfortunately.

JEANNE BLAKE: What about you? Would you get the vaccination if you could?

RESPONDENT 3: Yeah. I would definitely consider it. I mean, I'd have to do some research on it and talk it over with my doctor and see if it's right for me, but for the same reasons as her, pretty much. You never know what's going to happen.

JEANNE BLAKE: So you'd want to know about the potential side effects?

RESPONDENT 3: Exactly, yeah.

[END CLIP]

JEANNE BLAKE: Doctor, the woman who said she wouldn't put herself in that position, I didn't ask her whether she didn't have unprotected sex or whether she was in a monogamous relationship, but you say that condoms are not protective against HPV.

DR. CRUM: I think it is safe to say that condoms will not prevent HPV infection. Condoms are very effective at preventing HIV infection, but studies have shown that condom use in itself cannot be expected to prevent the transmission of papilloma virus, and young people out there should not expect that to be the case.

JEANNE BLAKE: It certainly doesn't mean that young people shouldn't use condoms if they're going to have sex, though. There are many other sexually transmitted diseases.

DR. CRUM: Absolutely. They have very good reasons for using condoms apart from the worries about papilloma virus.

JEANNE BLAKE: The other young woman said she would want to investigate what the potential side effects are. What do we know about what the side effects of the vaccination might be?

DR. CRUM: These vaccines are relatively early in their life history, if you will. There have only been a few studies so far. The one good aspect about these vaccines is that they're derived entirely from a viral product, if you will. So they're not being vaccinated with anything that comes from humans. Vaccines that are, let's say, impure or that might contain other products or even human proteins might be a great risk for someone, because you don't want to vaccinate them against something that they normally have in their body. But because the papilloma virus is a foreign protein, theoretically the vaccine should be relatively safe and so far has not been shown to have any serious side effects other than the usual pain at the site of injection.

JEANNE BLAKE: I'm sure that that will continue to be studied.

DR. CRUM: I'm sure it will be studied as these additional trials go forward. I'm sure they're going to be carefully monitored.

JEANNE BLAKE: The trials are continuing, so there is no vaccination available now, and it will be probably several years, yes?

DR. CRUM: That is correct. Merck is now moving toward a different strategy, I believe, in which they're going to vaccinate perhaps for several viruses at once. For some individuals it will be the viruses associated with genital warts, as well as type 16 and type 18, which is another cancer-associated virus. And so this is the nature of the next trial which is in program. This will be in several countries and will probably take two to three years to accomplish.

JEANNE BLAKE: All right. In the meantime, are there new technologies that women can hope for that will help clear up some of the false negatives and just improve the Pap smear technology?

DR. CRUM: As you can imagine, since papilloma virus is so closely associated with cervical diseases, they represent very good targets for prevention or at least for detection. And so HPV testing, as it's called, is now coming into popularity. Now, because so many young women are infected by papilloma virus that may not have anything wrong with them, just running out and testing every teenager for papilloma virus is not going to be very helpful. But certainly those young women who have Pap smear abnormalities that are not conclusive, for example if a young woman has a Pap smear

abnormality but has atypical cells, but they don't really know any more about it, doing HPV testing may be helpful. In some recent studies which have been done, and a very large recent conference which was held which was sponsored by a number of medical organizations, basically concluded that young women or any woman of any age who has an abnormal Pap smear that's inconclusive might benefit from HPV testing. The reasoning behind this is that if the HPV test were negative, then she would be eligible for a more conservative yearly follow-up, because if she's negative for HPV the chance of her having something serious is extremely remote. On the other hand, if she's positive for HPV, it doesn't necessarily mean she has something significant. Maybe only 20% of those women really need to be treated for a precancer. But nonetheless, that helps to free perhaps half those women from more close follow-up or the anxiety of further procedures at that time.

JEANNE BLAKE: One final question. We've only got another minute, but it appears that you support the idea of vaccination of those people that might be at the higher risk even though a small percentage go on to develop cervical cancer. You think it's worth the healthcare dollars to do that?

DR. CRUM: I think if you walked into a room of 70 women and you told them one of them was going to get cervical cancer in their lifetime and would all 70 be willing to vaccinate themselves to avoid being that one person, I'd expect most of them would seriously consider vaccination. And I think that's how you have to consider this type of therapeutic in this country. Certainly in another country where the rates are higher it would be much easier to make the decision. But I think that, given the risk that we face and given the fact that women go regularly for Pap smears and are regularly worked up and evaluated for abnormal smears despite a very low risk, I would think a vaccine would be a natural extension of that.

JEANNE BLAKE: It does seem to make sense. As you said in a New England Journal of Medicine editorial, one day you hope that cervical cancer will be a footnote in medical history in this country.

DR. CRUM: I certainly hope so, anyway.

JEANNE BLAKE: And I hope so too. Doctor, thank you for coming in to talk with us.

DR. CRUM: Thank you. It was a pleasure.

JEANNE BLAKE: I want to thank you for joining us on this edition of *About Health* TV. I'm Jeanne Blake, and I'll see you next time.

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