

Yale CANCER
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answers

WNPR Connecticut Public Radio



Hosts

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Building Awareness of Cervical
Cancer

Guest Expert:

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Gynecology & Reproductive Sciences*

Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and he is an internationally recognized expert on colorectal cancer. Dr. Foss is a Professor of Medical Oncology and Dermatology and she is an expert in the treatment of lymphomas. If you would like to join the discussion, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1-888-234-4YCC. This evening Ed and Francine welcome Dr. Peter Schwartz. Dr. Schwartz is the John Slade Ely Professor of Obstetrics, Gynecology, and Reproductive Sciences at Yale and Dr. Schwartz is internationally recognized for his work regarding cervical and ovarian cancers.

Chu Peter, thanks so much for being with us on the show this evening.

Schwartz Thank you. It's a pleasure to be here.

Chu Let's start off by defining what cervical cancer is.

Schwartz Well, cervical cancer is cancer that starts in the neck of the uterus. The uterus, for those who may not be familiar with anatomy, kind of looks like a pear or a light bulb and the narrow end, the part that has the threads on the light bulb or where the stem comes out of the pear, that's the cervix. Worldwide, cervical cancer is the second most common cancer women get, here in the United States though, it's only the 13th most common cancer. That's because our Pap Smear Screening Program works, where as in the underdeveloped world, we don't have an effective screening for cervical cancer.

Foss Can you tell us at what age women get cervical cancer and who is at risk for it?

Schwartz Women who are at risk for cervical cancer are women who have been exposed to the human papillomavirus. The factors that usually are associated with that are early age of first intercourse, multiple partners, and in the past, we used to talk about children delivered before age 18, but clearly the human papillomavirus is what is involved with the etiology of cervical cancer worldwide. Now, we should be careful when we talk about cervical cancer; we are talking about an invasive cancer. Invasive cancers can spread and kill patients, but many-many more women get precancerous changes which are the changes that we detect with the Pap smear, those are the changes that we can cure by treatment in the office or with some simple surgical procedures and we can preserve fertility. Invasive cancer of the cervix occurs mainly in women between age 40 and 50 here in the United States and that is the disease that the Pap smear screening has dramatically reduced.

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- Chu Now Peter, other than the human papillomavirus, are there any other risk factors that one needs to be concerned about?
- Schwartz Smoking has been a co-factor associated with cervical cancer and also alcohol consumption has been associated with cervical cancer, but the predominant factor associated with cervical cancer and the precancerous changes are the human papillomavirus infection.
- Foss Peter, can you tell us a little bit about human papillomavirus, how is it spread?
- Schwartz Human papillomavirus is a very interesting virus because it has a predilection for the anogenital area, that is the skin around the opening of the vagina as well as around the anus, and also for the mucous membranes, that's the lining of the vagina, and the cervix, but also it involves the upper airways as well and the digestive systems. The anogenital human papillomavirus that we are concerned about is spread predominantly through intercourse.
- Chu Obviously there has been a great deal of publicity surrounding the development of a vaccine for the human papillomavirus; can you tell us a little bit about that?
- Schwartz Yes, there is now one vaccine approved in the United States, but there are two vaccines that have been used worldwide. What we have recognized is that the most common types of human papillomavirus associated with invasive cancer of the cervix are type 16 and type 18. But we have also recognized that for warts that appear in the genital and the anal area, as well as cancers of the vagina and precancerous changes of the vagina, the vulva, and the anus, type 6 and type 11 are also associated with it. One of the vaccines, the type that is approved here in the United States, is called Gardasil and that one covers both 6 and 11, as well as 16 and 18. A second virus, which is used worldwide, is not yet approved in the United States; it only covers 16 and 18.
- Chu And again, when should the vaccinations be administered?
- Schwartz Well, the vaccine is approved for women ages 9 to 26, but we still think about age 11 or so is the time when young girl should be vaccinated. At this moment, it is only approved for women. It is not approved yet for men or for boys, although this seems to be in the works.
- Foss Peter, can you clarify for our listeners, if a person already has a positive human papillomavirus on their Pap smear, for instance, would they be a candidate for this vaccine, or is this only a preventive vaccine?
- Schwartz This is a preventive vaccine. There are basically two types of vaccines, there is a therapeutic

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vaccine, which will be used to treat a process, and therapeutic vaccine which is what the Gardasil is used to prevent the process, the infection, from developing. Now, the vaccine is approved for women who have not been exposed to HPV, but there are always issues such as, "What if I have a precancerous change?" Or perhaps, "I have type 16 and not type 18, can I benefit by being given the Gardasil?" We really don't have a lot of data on that, but it's something that could still be considered on a regular basis.

Chu Are there any potential side effects or complications resulting from the vaccine?

Schwartz Well, anytime we administer the vaccine, there is always local irritation; there can be pain, some burning sensation, or some itching in that area. There have been very few systemic problems that have been reported with the vaccine. There has been a rare case of asthma and case of bronchospasm, but in terms of mortality, which is what we are always worried about, the mortality rates for young women who have received the vaccine are no different than control groups.

Foss Given the risk of cervical cancer and the prevalence of HPV in the population, do you feel that this vaccine should become part of the regular immunization profile for our children?

Schwartz Absolutely, this has been the single most dramatic development in my 30 odd years as a gynecologic oncologist. The idea that a vaccine can be given to prevent what is a horrendous cancer, should it develop, just blows my mind. I recommended it for my own grand nieces now and I certainly think it is appropriate for young women.

Chu Peter, can we talk a little bit about the current methods approved for screening for cervical cancer?

Schwartz Sure. The Pap smear has been extremely effective in reducing the incidence rates of cervical cancer in the United States. They were introduced here in Connecticut in 1957 or so. We now expect only 120 cases a year of cervical cancer in Connecticut; in the United States as a whole, only 11,000 new cases of cervical cancer. When I went to medical school, it was a number one cancer in women, today, its number 13; Pap smear screenings really work. There have been some developments, however, in Pap smear screening, including the development of liquid based cytology, which initially was supposed to be more effective than the conventional cytology that women have been getting for many years. More recent studies suggest it's as effective as the conventional. So, it's getting the Pap smear that's critical, not the type that you get. Even more recently, however, has been HPV screening. HPV screening allows us to detect whether or not there is a so-called, high-risk oncogenic

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type of papillomavirus present. The high-risk oncogenic types are the ones that are associated with the development of precancerous and cancerous changes, whereas the low-risk oncogenic types are associated with warts. The introduction of the HPV DNA testing for women over age 30 has been quite beneficial and can allow one, if one has three negative Pap smears or negative Pap smears in association with negative HPVs, to prolong the interval between testing for cervical precancerous or cancerous changes.

Foss At what age should a woman start getting Pap smears and how long, say after menopause, does a woman have to continue the Pap smears?

Schwartz Well, it's just a bit controversial, but generally speaking, we recommend that within six months of a teenager beginning to have sexual intercourse, you should have a Pap smear. How long you should continue it has been debated a bit. Between the age of 60 and 65 have been the recommendations of our national organizations like the American Cancer Society. However, we are noticing that a lot of more women over age 50 are now being tested positive for HPV, and this group of women in particular are women who are divorced or lost their partner, and now have new partners. While we say 60 to 65, quite honestly, I see no particular upper limit that we should stop doing Pap smear screening at this moment.

Chu Take us through some of the process of the Pap smear. Are there any complications associated, what does it entail?

Schwartz Pap smears are a very benign test, but require that an instrument be inserted into the vagina to expose the cervix so that one can then use what we call a brush and simply wipe the cervix so that cells can sluff off the cervix and be captured either in liquid or a glass slide and that's the whole process and it's really very simple.

Chu It doesn't sound like there are really any significant side effects or complications that can occur from that procedure.

Schwartz No, but sometimes when one uses a brush on the inside lining of the cervix, you can see some spotting after you have had the Pap smear, it's not a reason to be alarmed, but it can occur.

Foss Peter, you talked about a woman in her 50s who is now HPV positive. Is there any role, say for a hysterectomy in such women, to prevent cancer in the future, or is Pap smear screening and following the patient adequate to prevent cancer?

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- Schwartz It gets very confusing as to what these abnormal Pap smears and these abnormal HPV testing's really mean to an individual patient, but in a postmenopausal woman who has a negative Pap smear but is HPV positive, meaning the high risk oncogenic type, she needs to be followed more carefully than somebody who has a normal Pap smear, but has no high risk HPV present, that woman should be still followed on an annual basis. If there is high risk HPV present, she needs to be colposcoped, and in particular, in postmenopausal women, the area of concern is called the transformation zone that's an area where the outside surface of the cervix, which is lined by squamous cells, meets the glandular cells of the canal. In postmenopausal women, this area recedes into the cervical canal and the colposcopy doesn't always pick up everything, but if the Pap smear is positive, that patient should be colposcoped and biopsied as soon as the report is available.
- Chu Can you just clarify one thing, is the HPV test a blood test, or is that a test done on the fluid that comes out of the Pap smear?
- Schwartz The HPV test is the test that's done on the fluid that's associated with the Pap smear itself. It's what's in the container after the doctor has taken the Pap smear.
- Chu I am just curious, is there any kind of blood test that can be done to help in this screening process?
- Schwartz Not currently.
- Foss What about prevention programs here in New Haven? The hospital participates in the National Breast and Cervical Cancer Early Detection Program, can you talk a little bit about that?
- Schwartz Yes, that program was originally started in 1990 and it was more of a screening and early detection program, but in the year 2000, a law was passed allowing the provision of Pap smears and mammogram for women who are either under a certain income level or are unable to provide any kind of health care. It's a free program and it allows for both the screening for Pap smears and also for a mammography, and since 2000, through Medicaid, it covers the payment of the services so that people can be treated free of charge. It's done through the State of Connecticut and Yale-New Haven Hospital was one of several hospitals in the state where this program was active.
- Foss It's great to hear that this is available to women across the state Peter. We would like to talk a little bit more in detail after the break about the treatment of cervical cancer. You are

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listening to Yale Cancer Center Answers and we are here with Dr. Peter Schwartz discussing the risks and the prevention of cervical cancer.

*Medical
Minute*

There are over 10 million cancers survivors in the US and the numbers keep growing. Completing cancer treatment is very exciting but cancer and its treatment can be a life changing experience. After treatment, the return to normal activities and relationships can be difficult and cancer survivors may face other long-term side effects including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers such as the Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has been a medical minute and you will find more information at yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut Public Radio.

Foss This is Dr. Francine Foss and I am joined by my co-host Dr. Ed Chu and Dr. Peter Schwartz, an expert in gynecologic cancers from Yale Cancer Center. Peter, we talked a lot about the risks for cervical cancer and the role of HPV, but what are the treatment options for a woman who has cervical cancer?

Schwartz Let's define what we mean by cervical cancer, because a lot of people are told they have cervical cancer when actually they have the precancerous change. For precancerous changes there are simple procedures one can do in the office, or in an outpatient surgery center, which remove a piece of the cervix; this is called a cone biopsy. It could be done in many ways; with a scalpel, a laser, or an electrolyzed loop called the LEEP procedure. However, when one has invasive cancer of the cervix, one has to be more aggressive. For early stage cervical cancers the standard treatment has been an operation called a radical hysterectomy, which not only removes the cervix but removes a border of normal tissue that surrounds the cervix; it also removes the upper vagina. For more advanced disease, radiation in combination with chemotherapy is the standard treatment for the management of cervical cancer.

Foss Is there any role, say for radiation, in some of these patient that have limited involvement who don't undergo surgery?

Schwartz For limited involvement radiation alone is not generally used; however, there is an operation called a radical trachelectomy and partial vaginectomy, which is being done here at Yale. This is an operation that is designed to hopefully cure cervical cancer and preserve fertility. That operation would be used in a select group of younger aged women.

Chu Would a woman typically go to their general GYN physician for these treatments that you

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are talking about, or would that individual seek medical care from a specialist like yourself, a GYN oncologist?

- Schwartz For the precancerous changes called cervical intraepithelial neoplasia, our community doctors are trained to take care of that, and that's where the overlying majority of patients receive care with community doctors in our community hospitals. For invasive cancer of the cervix, that's a different situation, and that's where they need to see a gynecologic oncologist.
- Foss What is the role of CAT scanning, PET scanning, and MRI scanning in women who have invasive cervical cancer in terms of making a diagnosis and a treatment plan?
- Schwartz We diagnose by simply biopsying in the office, and that gives us the diagnosis of an invasive cervical cancer. Once we have that diagnosis, then the question is how far has the disease spread? If in the office, using a physical exam by a gynecologic oncologist, the disease seems to be limited to the cervix, we often don't do much more diagnostic evaluation. However, if the disease seems to extend beyond the cervix, then diagnostic imaging is important. The CAT scan can be very helpful in telling us whether or not there is disease involving lymph nodes, particularly along the para-aortic area. It will help us to tell whether the urinary tract is in anyway involved; we look for things like ureteral obstruction, deviation, and duplication. The MRI is much more effective in looking directly at the local area of the pelvis, and it tell us whether the disease has extended outside of the cervix and it can certainly look very well at the pelvic lymph nodes and tell us whether or not there might be involvement. The PET scan is generally used to identify more distant spread. So, in early stage cervical cancer, very limited imaging is necessary, in a more advanced stage, that's where these other imaging modalities really come into play and that's how we use it.
- Chu Peter, is there any role for chemotherapy, giving chemotherapy drugs either before surgery is performed or perhaps giving chemotherapy drugs once the surgery has been conducted?
- Schwartz Giving chemotherapy before definitive surgery is done or radiation is done is called neoadjuvant chemotherapy, and its something that has been going on for certainly at least the last 25 years in cervical cancer management. This is particularly because in the third world, they see a lot more advanced stage disease then we see. Neoadjuvant chemotherapy is most effective in something called stage 1B2 cervical cancer. This is when the cancer is really expanding the cervix beyond 4 cm, but hasn't spread outside of that area. It would appear that neoadjuvant chemotherapy can shrink the cervix down and then allow the surgeons to do radical hysterectomies. So that's the one place where neoadjuvant chemotherapy appears to be effective. Once the diagnosis is made and radiation is going to be given, cisplatin

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chemotherapy is usually given as a single agent on a weekly basis. There have been four different studies that have shown that for patients receiving primary radiation therapy, platinum-based chemotherapy in combination with radiation is the most effective way to treat people. There has been a study that showed for those women who have had radical hysterectomies, but have bad prognostic features when the pathologist examines the specimen, those patients who would then get postoperative radiation if one adds chemotherapy, also benefit from the combination of the chemotherapy with platinum, cisplatin and the radiation.

Foss What are the complications for women of having a combination of chemotherapy and radiation?

Schwartz The complications don't seem to be increased significantly. What the issue with radiation is that it can irritate the bowel and it can irritate the bladder. Typically patients who receive radiation or chemoradiation tend to have loose stool and diarrhea, which during radiation therapy the real therapist will put them on diet and give them medications to control that. They also will have to void, pass urine more frequently during the radiation. For the most part, that clears following completion of the chemoradiation.

Foss What about the role of biological agents? We have heard a lot of about the HER2/neu antibodies, and breast cancer, and the antibodies that are targeting the EGF receptor, and various kinds of solid tumors, do any of those apply to the treatment of cervical cancer?

Schwartz At this moment, to my knowledge, there are none approved; however, there is a research program that is being conducted by the Gynecologic Oncology Group, which is now an international study group but its based in the United States, and we are participants in the GOG study and are looking at EGFR its epidermal growth factor receptor inhibitors in recurrent cervical cancer. It's still experimental at this point.

Chu Peter, how significant a problem is a recurrence of cervical cancer?

Schwartz Well, it's a real problem. Basically, in Connecticut, we see two groups of women. One who have had fairly reasonable Pap smear screening surveillance and they tend to be found with early stage cervical cancer and are usually cured with a radical hysterectomy. Then we get another group, and it's the larger group of women, who have declined to have Pap smear screening; they come in with invasive disease that's advanced. Early stage disease, stage I disease, has roughly a 90% cure rate. Once we start to see that the disease has spread outside of the uterus, the cure rates decline dramatically. When the spread is just limited outside the pelvis, stage 2B, it has about a 60% cure rate, when its spread to the pelvic sidewalls, stage

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3B, then we are talking about between 30% and a 50% cure rate, which means that 50% to 70% of the patient's are going to recur. And with stage IV disease, which we still see in Connecticut, in women who have neglected to have Pap smears, almost every one of them is going to recur.

Foss When we talk about neglecting to have Pap smears, we probably should have talked about this at the beginning, but are there any symptoms that those women experience? If you just go on without a Pap smear and you are developing cervical cancer, how would you know?

Schwartz That's a great question. Typically, the belief of gynecologists was that women with invasive cancer have symptoms, and women with pre-invasive disease don't have symptoms. Women with invasive disease experience bleeding because the tumor grows and outstretches its blood supply, and they tend to bleed. They can have vaginal discharge, and this is due to secondary infection by the bacteria in the vagina that causes malodorous discharge. They can also have pain as the tumor invades the nerves in the pelvic sidewall and pain can radiate down their legs; sciatic pain is classic with advanced stage cervical cancer. We did a study, however, looking at precancerous changes in the cervix and early cervical cancer, and we found that about the same proportion of our patient's had bleeding spontaneously or after sex, who had carcinoma in situ which are precancerous changes, one step before invasive cancer. So, abnormal vaginal bleeding, particularly bleeding after having intercourse, is a very-very serious warning that there could be a problem of cervical cancer or precancerous change.

Chu What percentage of women, in the State of Connecticut and in the United States, still are not getting screened for cervical cancer?

Schwartz Back in the 1980s we reported on women who had cervical cancer who had been getting annual Pap smears and had what we call rapidly invasive cervical cancer. That led to a very large program project where we looked at every case of cervical cancer in Connecticut between 1985 to 1990, and what we found was that the invasive cancers, about 25%, occurred in women who had Pap smears that were read as normal within three years of the diagnosis of cancer. 75% either had not had Pap smears or had stopped having Pap smears once they had delivered their last child. So, we found that a large percentage of patients who developed the cancer don't have Pap smears, what we don't know is overall how many women don't have Pap smears.

Chu Do you have a sense of, in 2009, if we have gotten better in terms of bringing down that number from 75% to hopefully a much lower number?

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Schwartz I don't have a feeling that it's changed very much, to tell you the truth. When I look at what goes on in our service, I think that this is the best reason for Gardasil, for the cervical vaccine.

Foss In terms of understanding the biology of these kinds of cancers, GYN cancers, I understand that you have a very active research program in your department called Discovery to Cure, can you tell us a little bit about that?

Schwartz Well, the Discovery to Cure program it is about ten years old now. It was originally designed to study ovarian cancer, then we moved into uterine cancer, and now Dr. Alessandro Santin has joined faculty. Dr. Santin is, among many other things, interested in vaccine therapy for cervical cancer. He is in a phase II trial now looking at a vaccine that he has developed for cervical cancer. So, the Discovery to Cure program is marching on and we are taking on more and more diseases as we are able to afford investigators and laboratory research.

Chu And are there any clinical trials that you and your colleagues are currently involved with focusing on developing new therapies for say, advanced recurrent cervical cancer?

Schwartz At this moment the only one that we are actively involved with is the gynecologic oncology group trial that uses molecularly targeted therapy, and Dr. Santin is the principal investigator for the gynecologist oncology group in that trial.

Foss And as we get close to summer, I just wanted to put in a plug for your program, because I know that you do take on high school students to work in the research labs along with senior investigators and that is a tremendous program, hopefully to interest some young people in going into science in the future.

Schwartz Exactly right, it's a great program. Dr. Gil Mor runs that program now for us and is supported through the Discovery to Cure mechanism. It's just one of the things; we are not only interested in laboratory research, we are interested in education. It starts in the high school, and we have college students as well working in the lab, medical students, and graduate students. It's a lot of information that we try to provide to a lot of different people.

Chu It's amazing how quickly the time has gone. Peter, we look forward to having you back on a future show to give us an update on what's going on with cervical cancer and all of the other GYN cancers that you are involved in.

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Schwartz Thank you very much. It's a pleasure.

Chu You have been listening to Yale Cancer Center Answers and we would like thank our special guest expert Dr. Peter Schwartz for joining us this evening. Until next time, I am Ed Chu from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions or would like to share your comments, go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.