Yale CANCER CENTER answers

WNPR Connecticut Public Radio

Cervical Cancer Screening and Prevention

Guest Expert:
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Yale School of Medicine

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Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Miller is an oncologist specializing in pain and palliative care. 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 Dr. Chu welcomes Dr. Peter Schwartz. Dr. Schwartz is the John Slade Ely Professor of Obstetrics and Gynecology at Yale school of Medicine and a leading expert on cervical cancer.

Schwartz Worldwide it is extraordinarily important because it is the second most common cancer women experience in the world. There are roughly 500,000 new cases a year, and about 275,000 of those women will die. Looking at this on an international basis, it is an extremely important cancer. Only breast cancer in women occurs at a greater frequency.

Chu It looks like the distribution of cervical cancer has changed. It seems not to be so much an issue in the developed countries, but perhaps more of an issue in the underdeveloped ones.

Schwartz Absolutely correct. In developed countries where Pap smear screening is routinely available, the incidence of cervical cancer has been dramatically reduced. In turn, in countries where cervical Pap smear screening programs are inappropriate for either cultural reasons, or they simply are not available because of the cost, these are the areas where incidence of cervical cancer is still very high.

Chu What is the typical age in which we might see cervical cancer present?

Schwartz Cervical cancer is a disease of younger women. The peak age incidence is age 40 to 45. The precancerous changes we generally see about 10 years earlier. Carcinoma in situ of the cervix is the most advanced precancerous change and that peaks around age 35, so we generally think of it as a 10-year period of time that the cancer goes from pre-malignant to an invasive cancer phase.

Chu What are the main risk factors for cervical cancer?

Schwartz Traditionally they have been related to sexual activity. The greater number of partners one has is certainly the most significant epidemiologic factor, which seems to all be related to the human papillomavirus exposure.

Chu As I understand there are a number of different types of papillomaviruses, is that right?

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Schwartz That is correct. There are well over 100 human papillomaviruses that have now been identified, but there are 15 that have been associated with cancer of the cervix specifically.

Chu Are there any racial disparities related to cervical cancer?

Schwartz Yes, there definitely are. In the United States, we estimate that among the Caucasian and Hispanic-Caucasian population, it is about 20 per 1000, whereas among the African-American population, it is about 30 per 1000 that will have an HPV infection.

Chu African Americans seem to be at a higher risk for developing the disease.

Schwartz That is correct.

Chu Just as background, what are the typical types of symptoms that a woman might present with?

Schwartz Invasive cervical cancer has been thought not to have symptoms early when it is confined to the cervix, but in studies that we have done here at Yale, and others that have been done as well, we have found bleeding, discharge and pain as symptoms that we see with cervical cancer. Even with early stage cervical cancer one can have abnormal discharge and bleeding. We did a study about a decade ago where we looked at precancerous changes, and much to my surprise, about 70% of the women with carcinoma in situ of the cervix had vaginal discharge or bleeding, something that we do not routinely think is associated with those precancerous changes.

Chu What should a woman do if she has any of the symptoms that you just outlined?

Schwartz With such symptoms she should promptly be seen by a gynecologist, and that is really critical. Even if she has routine gynecologic healthcare performed, if she starts having abnormal discharge, bleeding and certainly pain, she needs to see a gynecologist promptly.

Chu What would that gynecologist do in terms of the evaluation process?

Schwartz The initial evaluation would be a physical examination and of course a pelvic examination would be an intricate part of that evaluation. In general, a Pap smear would be done. If there is an obvious change, that change on the cervix should be biopsied.

Chu You have already mentioned the Pap smear which is a diagnostic test to look for cervical cancer. Can you tell our listeners a little bit more about that test?

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Schwartz The important take-home information for our listeners is that Pap smears work. Pap smears were introduced in Connecticut, and across the nation actually, in about 1956-1957. They were around prior to that, but not accepted for screening programs. Around 1956-57, cervical cancer was the most common cancer of women in the United States. Today, it is number 13 in the list of incidence of cancer in women. This is due to the Pap smear which makes a huge difference. The Pap smear is an integral part of women's health on a routine basis. As a matter of fact, this month is cervical cancer month, and our Lieutenant Governor, Fedele, visited with 4 of the hospitals in Connecticut this past week promoting Pap smear screening. It really does work, and it is very important that all women understand that.

Chu When should women start having Pap smears done?

Schwartz The general recommendation is within a year or two of becoming sexually active, and certainly by age 21.

Chu Then how frequently should they be getting Pap smears?

Schwartz An annual Pap smear should be a routine part of women's health. We have now introduced human papillomavirus screening along with Pap smears, and that is only recommended for women over age 30 on a routine basis. The reason why it is for women over age 30, is that many women in their 20s have human papillomavirus exposure and their body's own immune system will eliminate it. About 45% of women age 20 to 24 are positive for HPV in one of our national studies that looks at the population of the Unites States as a whole. 45% of women in the 20- to 24-year age range are positive for HPV. Once a woman gets to the age 30 and over, the body's immune system has usually fought off human papillomavirus. This is when it becomes valuable in screening. If you combine the Pap smear with HPV determinations and the Pap smear is unremarkable and your HPV determination is free of high oncogenic-type HPVs, that is the HPV types that are associated with precancerous and cancerous changes, then it is recommended to go to a 3-year basis for Pap smears in combination with HPV testing. Pap smears alone we would do on an annual basis in women who are sexually active.

Chu Until what age?

Schwartz It is generally recommended to about age 60 or 65 by a number of our national societies. Certainly, I have no objection to continuing that on an indefinite basis, but one should know that it is generally recommended, that if you had normal Pap smears on an annual consecutive basis and HPV negative, that once you reach that age it is highly, highly unlikely that anyone is going to get cervical cancer.

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Chu And the HPV test is a blood test?

Schwartz No, it is done with Pap smear screening.

Miller So it is done on the fluid or the tissue that is obtained?

Schwartz Yes, that is correct. We can do it either with liquid-based cytology or if we use the conventional old style Pap smear, one does a separates swab and sends that off for HPV detection.

Miller One of the real significant advances over the last couple of years has been the development and implementation of the HPV vaccine. Can you tell our listeners a little bit about the value and importance of that vaccine?

Schwartz Certainly. In my entire career, I can imagine no change or no development that has been more important than the HPV vaccine. It is really extraordinary, the whole idea that you can vaccinate someone and potentially prevent 70% of the most common cancers of the cervix. It just blows my mind. The critical thing is that the HPV vaccine, as it currently is being used, should not necessarily be given to people already exposed. Since women are being exposed at very early ages, 25% of the population between age 15 and 19 in the national trial I mentioned before are HPV positive, one has to start at a very early age to administer the vaccine in order for it to be effective. The FDA is recommending that youngsters between age 9 and 11 be vaccinated, because if they have already been exposed to the HPV virus, it is not going to be effective against that strain of virus they may have been exposed to. About 55% of cervical cancers are associated with type 16 HPV, and another 15% are associated with type 18 HPV. The only available HPV vaccine can immune the young women from getting HPV 16 or 18 type infection. And that is impressive.

Chu That is very impressive. How many injections does it typically take?

Schwartz It is three injections currently. The vaccine currently available is given initially, and then at 2 months and at 6 months after the initial vaccination.

Chu You say young girls at the age of 9 to 11 will be getting this vaccine; that seems kind of young.

Schwartz The data is really remarkable. Once you reach about age 12, sexual activity increases significantly and that has been documented with HPV typing of these young women. They are sexually active, they are getting exposed to HPV at very early ages and we really need to administer it to these 9- to 11-year-olds.

Chu Any side affects, either short-term or long-term, that have been identified to date?

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Schwartz Anytime you give a vaccine there is a little sting from the injection of course. Sometimes there can be some chills and fever, usually they are very short-lived and it has not been a major problem. As far as major problems, there has been a rare case of asthma associated with it. It is not frequent enough to prohibit one from getting the vaccine.

Chu Okay great. Well, we would like to remind you to e-mail your questions to canceranswers@yale.edu or call 1-888-234-4YCC. We are going to take a short break for medical minute. Please stay tuned to learn more information about cervical cancer with our special guest expert, Dr. Peter Schwartz.

Medical Minute

The American Cancer Society estimates that in 2008, there will be over 62,000 new cases of melanoma in this country and about 2,400 patients are diagnosed annually here in Connecticut alone. While melanoma accounts for only about 4% of skin cancers, it causes the most skin cancer deaths and when detected early melanoma is easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive cancer centers such as the Yale Cancer Center to test innovative new treatments for melanoma. Patients enrolled in these trials are given access to newly available medicines which have not yet been approved by the Food and Drug Administration. This has been a medical minute, and you will find more information at www.yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut Public Radio.

Chu Welcome back to Yale Cancer Center Answers, this is Dr. Ed Chu. I am here in the studio with my special guest expert Dr. Peter Schwartz talking about the diagnosis and treatment of cervical cancer. Before the break, we were talking about the wonders of this HPV vaccine and the critical importance of Pap screening and testing. Peter, you and the folks here at Yale Cancer Center are also part of the National Breast and Cervical Cancer Early Detection Program. What is this program and who is eligible?

Schwartz This is a wonderful program because it offers free mammography and Pap smear screening for women who cannot otherwise afford to have a Pap smear. It is a great program that has picked up cervical cancer and it allows women to be tested and then receive treatment. It is a very important program. There should be no excuse, certainly no financial excuse, for not having a Pap smear. Here in Connecticut it is absolutely available to everybody.

Chu Great, that is terrific. Along those same lines, what about the HPV vaccine. Are there are any provisions made for people who are less fortunate and may not be able to afford the vaccine?

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Schwartz I am not familiar with the program at the state levels, so I better not say anything that I am not familiar with.

Chu We would hope that just like with Pap smear screening, there are provisions made for young girls to have access to something that can save lives.

Schwartz Yes, certainly.

Chu So once a woman is diagnosed with cervical cancer, what are the different ways that you think about treating that patient?

Schwartz Generally speaking the management of early-stage cervical cancer is to remove it surgically. The treatment of advanced-stage cancer is to treat it with a combination of radiation therapy and chemotherapy. Now, there are certain hedges that we really have to make. You and I talk about cervical cancer and we know what we are referring to, but at lot of times precancerous changes are interpreted by the patient as being cancer. Those precancerous changes do not require the aggressive treatment that an invasive cancer requires. Cancer kills people, and the treatment requires either the removal of the cervix along with the rim of normal tissue and the draining lymph nodes to the cervix, those are lymph nodes along the pelvic sidewall, or it requires radiation that covers the field of the cervix, the uterus, and the draining lymph nodes. One way or another, the entire area of the cervix and the regional draining lymph nodes must be covered to be successful in its management. The general rule of thumb is that a younger patient who undergos surgery can preserve ovarian functions, whereas for a woman who is already postmenopausal, that would be much less of an issue. Radiation and surgery have quite opposite effects which we discuss with our patients when we are talking about management. Basically, if we use surgery, one can have some urinary tract dysfunction and some intestinal tract dysfunction; usually constipation which I see with the intestinal tract and sometimes a lack of sensation of the need to urinate is a side effect of the surgery. In turn radiation causes irritation, and we get the opposite effects; the bladder gets irritated and you have to pass urine more frequently, the bowel gets irritated and you can have loose stool and diarrhea. There are side effects and you have to be aware of them.

Recently, within the past decade, it has been very obvious that if we give radiation we can enhance the radiation effect by giving chemotherapy in combination with the radiation. The standard chemotherapy that we give today is cisplatin. There are some research trials that Yale is involved with through the gynecologic/oncology group and currently we have a trial with tirapazamine plus cisplatin for patients getting radiation therapy for cervical cancer. That is being compared to the standard, cisplatin and radiation therapy. For younger age women, there are now opportunities to not only preserve ovarian function, but to preserve reproductive function. An operation called a radical trachelectomy is now being performed where the uterus is preserved and the ability to have

children is preserved. What happens there is that the uterus has 2 parts, generally speaking, one is called the body of the uterus, the corpus, and that is the part that is preserved. The narrow part that protrudes into the vagina is the cervix, and one normally removes about two-thirds of the cervix along with the upper third of the vagina and soft tissue around the vagina, and that allows one to then preserve uterine function and women can have children. The only problem with that procedure is that there is a high rate of premature delivery, so one has to be aware of that when choosing that option.

Chu Peter, in your experience, do you typically see women who present with early-stage cervical cancer or more advanced stages of cervical cancer?

Schwartz We actually see both; it is about 50-50. As a matter of fact, one of the landmark studies was actually done at Yale with the school of Epidemiology and the Department of Obstetrics and Gynecology working together. We could not figure out in the mid 1980s why women were still getting cervical cancer. We had Pap smear screening, yet we were still seeing it. We did the first really outstanding epidemiologic study where we looked at every woman with cervical cancer in Connecticut over a 5-year period of time. We thought we were going to find laboratories that were making errors in reading Pap smears, but that was not the case. What we found was that at least half of the women with cervical cancer had not had a Pap smear ever, or had gone at least 5 years without having a Pap smear. Those generally were more advanced stage disease patients that were avoiding healthcare until the discharge or the bleeding or the pain overwhelmed them and they had to seek aid. Then we saw another group of patients who were young, had annual Pap smears, and still developed cervical cancer. We are puzzled by that, and we remain puzzled by that. We have done HPV studies on these women working with the National Cancer Institute. We cannot give you an answer today why somebody can have absolutely normal Pap smears and still get cervical cancer within a year of the last normal Pap smear. It does occur.

Chu It seems like a very short time interval. A Pap smear with absolutely no kind of dysplastic changes?

Schwartz That is absolutely correct. These were reviewed by experts. We got involved with HPV typing at an early time and we still cannot explain it. That is why I go back to our earlier statement; abnormal discharge, bleeding or pain must be evaluated promptly. The Pap smear is terrific. It is the best screening test we have for cancer, but it is not perfect.

Chu Your group has really focused on trying to bring the laboratory research findings into the clinic. You have a program, which you really founded, called the Discovery to Cure Program. It is a beautiful example of bench to bedside, bedside to bench research. Tell us a bit more about that.

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Schwartz The Discovery to Cure Program originally focused on ovarian cancer, which is the major pelvic cancer health hazard for women in the United States. There are more deaths from ovarian cancer than from all the other cancer sites combined in the pelvis. We have expanded and we are studying endometrial cancer. I am very pleased to tell you that we have recruited Dr. Alessandro Santin who is currently at the University of Arkansas. Alessandro will join us in March. Alessandro is actively involved in developing a therapeutic vaccine for the management of cervical cancer. The vaccine that we have been talking about is currently available in the United States and is a prophylaxis vaccine, a vaccine that has to be given to women before they are exposed to the HPV virus. Alessandro is well on his way to developing a vaccine to treat people who have had cervical cancer and we are very anxious to have him join our faculty. We, of course, are interested in women's health, but I must say that although one thinks about HPV as being associated with cervical cancer, it seems that it is associated with a number of other cancers. For us in the world of gynecology, there are precancerous and cancerous changes of the vulva and the vagina that are important. Precancerous changes of the anus, that often are associated with precancerous changes of the vagina and cervix, are very important, but anal cancer is associated with HPV. Oropharyngeal head and neck cancers are also associated with HPV. We think that Alessandro may play a much broader role in his research work with therapeutic vaccines then just being focused exclusively on the gynecologic reproductive organs in the pelvis. The Discovery to Cure Program is growing. We have had some wonderful developments here at Yale in terms of the management of ovarian cancer. One of the drugs, Phenoxodiol**,** which was developed through the work of Gil Mor our chief scientist in the program, has also been used for cervical cancer treatment. We have just completed accruing the last patient to that study and it appears that there is some activity with the Phenoxodiol in treating woman with cervical cancer. We will have to wait and see what the final results are, but it is something that we are excited about and may very well go into a national program for evaluating this drug as a way of enhancing treatment for cervical cancer. This is all done through the Discovery to Cure Program.

Chu Your group has been looking at biomarkers for ovarian cancer. Have you thought about perhaps expanding and extending your studies to look at biomarkers for cervical cancer?

Schwartz I am sure that Dr. Mor's work has established a paradigm for evaluating biomarkers for all cancers. His work in the Discovery to Cure Program and his own research is being looked at for a variety of other sites. I was just at a meeting last week where Dr. Mor and Dr. Michael Schneider were quoted. They have published some papers showing a profile of antibodies in serum that may be profiles that we can use to determine whether or not certain cancers are present. It is a different sort of biomarker approach and we are definitely going to explore

this a little further as well. Cervical cancer is often associated with a lot of inflammation, so I am sure that these antibodies will be highly expressed.

Chu — Fascinating. We look forward to hearing more about that. In the remaining couple of minutes, are there are any other clinical studies that you might want to highlight for listeners out there?

Schwartz — While I have a couple of more minutes, let me go back to Pap smear screening because I do not want any mistakes made about what this vaccine is going to do about reducing Pap smear screening. That is not the intent of the vaccine. The vaccine is going to be given mainly to women age 9 to 11. It is going to take 20 years from now before we may see the effect of the vaccine against cervical cancer in these youngsters. Women must continue to get their annual Pap smears. Even women who are vaccinated will only theoretically be protected against the 70% of HPV types associated with invasive cancer, not the 30% that are not. I do not want to leave the studio without really emphasizing the point that Pap smear screening is extremely effective, and it is vital that young women know they must continue to get their Pap smears.

Chu — As you say, an annual Pap smear is critical because if you have a few negative ones and say, "Well, I do not have to worry about cervical cancer", then you wait a while and do not have any pap smears, then you've developed advanced cervical cancer.

Schwartz — Absolutely, and our study has been reflected in subsequent studies nationwide. Fifty percent of women with cervical cancer had stopped having pap smears within at least 5 years from the time of the diagnosis of cervical cancer. Many have never had Pap smears at all, so it is widely important. The message for today is Pap smears work, keep getting them.

Chu — That is a great take-home message, Peter. Thanks so much for joining us this evening on Yale Cancer Center Answers. Until next week this is Dr. Ed Chu from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions, comments, or would like to subscribe to our Podcast, go to www.yalecancercenter.org where you will also find transcripts of past broadcasts in written form. Next week, you will meet Dr. Bernie Siegel, the author of Love Medicine and Miracles.