

Yale CANCER CENTER *answers*

WNPR Connecticut Public Radio



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Gynecological Cancers

Guest Expert:

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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associated Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale New Haven. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This week, Dr. Chagpar welcomes Dr. Peter Schwartz. Dr. Schwartz is John Slade Ely Professor of Obstetrics, Gynecology, and Reproductive Sciences and Vice Chair of Gynecology at Yale School of Medicine. Here is Anees Chagpar.

Chagpar Let us start off by having you tell us a little bit about yourself, how long you have been at Yale, how long have you been practicing in this field?

Schwartz I am a gynecologic oncologist, which means I take care of women who have cancer in the pelvic reproductive organs. A gynecologic oncologist will not only do surgery, they will do chemotherapy as well as work as a team member in radiotherapy treatments. I started back in 1973 when I did a fellowship at MD Anderson Hospital. It was a two-year fellowship and then I joined the faculty at Yale in 1975.

Chagpar Wow! Receipt

Schwartz I have been there ever since.

Chagpar Let's talk a little about what is the latest and greatest in gynecologic cancers? Tell us a little bit about what those kinds of cancers are, what treatments are available, and where the field is going?

Schwartz Sure, so the most common cancers that women get of the pelvic reproductive organs are cervical cancer, uterine cancer, and ovarian cancer. When I started out in my medical career, cervical cancer was the most common cancer that we saw. Today, it is number 13 and that is all due to Pap smear screening, conventional Pap smear screening. Uterine cancer, cancer that develops in the body of the uterus, is the most common cancer and it has the greatest survival rate because it is associated with the obvious early warning signal of postmenopausal bleeding, so 90% of uterine cancers occur in postmenopausal women and bleeding is the sign that leads them to come in to be treated. About 70% of uterine cancers present as stage I disease, and it is highly curable with a hysterectomy as the basis for the treatment. The most concerning of all the cancers now is ovarian cancer. The incidence of ovarian cancers has remained the same over many years and the prognosis for ovarian cancer still remains poor. While we have been able to prolong survival dramatically with modern treatment efforts, the overwhelming majority of the patients that present with stage III or IV disease, disease that has spread into the upper abdomen or beyond the

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abdominal cavity, our treatment overwhelmingly turns out to be palliative rather than curative. Going back to cervical cancer, 50% of patients now present with stage I disease. These are patients who routinely have Pap smear screening and it is found as an incidental finding, although sometimes it can be associated with either discharge or abnormal bleeding. Treatment for cervical cancer had been, for stage I disease, an operation called a radical hysterectomy. We are starting to learn that there are patients who do not need such a radical procedure and indeed for women in the reproductive age who would like to preserve fertility and who have relatively early stage I cervical cancers, a procedure called a radical trachelectomy and partial vaginectomy allows those women to preserve fertility. This is an exciting development and this operation is being done at Yale. For uterine cancer, the overlying majority of women seem to know to come in when they have abnormal or postmenopausal bleeding, so the operation that we favor there is to remove the uterus, the tubes, and ovaries as well as pelvic and paraaortic lymph nodes. We have learned over the many years that I have been in gynecologic oncology that uterine cancer spreads through the lymphatic primarily, not through the blood stream, and by taking out the lymph nodes we can identify who has more advanced disease and we can modify our treatment accordingly. Uterine cancer is one of the cancers where radiation therapy is playing a lesser role for advanced disease and chemotherapy is playing a much more important role as prospective randomized trials are now showing superior survival using chemotherapy over the conventional radiation therapy that had been used in the past. With ovarian cancer, we keep on finding new agents that have activity in the disease, but the basic treatment for the disease remains upfront surgical cytoreduction, meaning that we take patients to the OR and we remove as much cancer as possible. We have now learned that leaving any cancer behind limits survival, so when we now talk about so called optimum surgical cytoreduction, we talk about removing all of the disease that a surgeon can see or find. This can mean removing a number of organs, the intestines, the large or small bowel is often resected in this disease to remove all of the cancer and at times the diaphragm has to be stripped of any cancer on it, or resected, and indeed in more advanced cases, splenectomies and partial distal pancreatectomy have to be performed. Interestingly, we started using a procedure called neoadjuvant chemotherapy at Yale in 1979 in one of my patients where we simply could not get her to the operating room, she was too ill and I desperately tried something, the use of cisplatin which had become available commercially that week along with Adriamycin, a drug that had been available since 1974. So in 1979 our first patient was treated with neoadjuvant chemotherapy and she lived 12 years disease free before she finally succumbed to a cardiac event. That started the program at Yale of neoadjuvant chemotherapy that was slowly adopted in the United States but more rapidly adopted in Europe. There is now a prospective randomized trial that was published in the New England Journal of Medicine two years ago that showed that neoadjuvant chemotherapy, giving the chemo before you do the surgery, is as effective as doing aggressive upfront surgery followed by the chemotherapy. The advantage of the neoadjuvant chemotherapy is that there is much less cancer present and so the surgery is much less radical, although it still can

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be radical. Our patients go home in five to six days after neoadjuvant chemotherapy has been given and surgery is done. Our patients go home after 11 days when we do upfront surgical cytoreduction, so there is less blood loss, less intensive care unit stay, shorter hospitalizations and the same survival. What we are now working on is trying to individualize care even further. We are working with Gil Mor on a new protocol that will be available, we hope, very soon, where we will determine the chemotherapy agents to be used based on molecular biological features of the cancer cells that we will get from fluid that is in the patient's abdomen or in the chest and that will tell us not only who gets the neoadjuvant chemotherapy, but which agents may be more effective in the management of the disease. So that is kind of the flavor of the three major cancers. Cervix, significantly less from number 1 to number 13, for uterine cancer early detection has been critical and for ovarian cancer there are new approaches using the same chemotherapy but giving it first before surgery and that seems to have had a significant effect at least in the quality of life our patients have had.

Chagpar That is fantastic, especially hearing the story about what has become standard of care and what is such a phenomenal advance in terms of the management of some patients, starting with your patient so many years ago and to hear about some of the trials that are going on at Yale. Tell us a little bit more about this study with molecular markers? Is that what people talk about in terms of personalized medicine?

Schwartz Yes, this is exactly what it is and we are doing it not only in ovarian cancer, but we are also doing it in a very aggressive form of uterine cancer called uterine serous cancer. It has also been known as uterine papillary serous cancer, but it turns out that not all of the cancers are papillary, that is the appearance under the microscope. Dr. Alessandro Santin has really led the effort with the uterine serous cancers and he has now done genomic studies at Yale and has identified potential new approaches using molecularly targeted therapy because he has identified very specific aberrations in the genes of the cancer cells that make up this uterine serous cancer. Now, this cancer is a new cancer by our standards, it was only discovered and recognized in 1980, but when it was identified it represented only 10% of all stage I cancers of the uterus, but 50% of all the deaths from uterine cancer, so this is a very aggressive cancer and Yale has been setting a national pace for management of the disease. We have published more papers than any other single institution in the country and this is a reflection of unknown epidemiologic reasons. We certainly would like to understand more why in Connecticut we are seeing this disease. This is particularly strange because the usual factor associated with uterine cancer is obesity. And if you look at the national statistics, except for Colorado, Connecticut is the thinnest state in the country.

Chagpar That is fantastic, but I think much of that population may have to do with the excellence that you have at Yale and the programs that you have, which may be drawing people to the program here.

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Schwartz I am sure that is true now, whether it was true when we started out I cannot be sure because it was a newly recognized entity and we just seemed to have a larger experience. So, we are looking at molecularly targeted therapy in this disease. We actually have an active protocol that uses

Herceptin, a molecularly targeted agent along with conventional chemotherapy in what we call a prospective randomized trial and we now have about 12 institutions that have joined our multi-institutional trial for this disease.

Chagpar Let us switch gears a little bit and talk about some of the products of randomized control trials and a lot has come out in the news over the past several years about a vaccine for cervical cancer. Is that used? Can you tell us a little bit more about that and how we can prevent cervical cancer?

Schwartz Yes, I think it is very important to understand that the vaccine that commercially is available, FDA approved, is a vaccine to prevent pre-malignant changes in the cervix and cervical cancer and the vaccine also prevents vaginal or genital warts. There are roughly 12,000 new cases of cervical cancer found in the United States each year, here in Connecticut only about 100 cases in the entire state. And this is because of Pap smear screening, but if you look throughout the United States, about 300,000 women will develop what we call carcinoma in situ of the cervix, or CIN 3. Over a million women are expected to develop papillomavirus infections of the cervix and over a million women a year will develop genital warts. Warts and premalignant changes of the cervix, human papillomavirus infections, all can be prevented by immunizing young women before they are sexually exposed.

Chagpar Is that a program that is available at Yale, and which women would you recommend? Is there an age at which you start or an age that is too early to start?

Schwartz Fortunately for the public, this is available at any pediatrician's office or general practitioner's office, so the vaccine is readily available, it is recommended to be given to young women between ages 9 and 11, but is approved up to age 26 at this point. The problem is that frankly none of us know when a young woman is going to become sexually active. Certainly in the 15 age range at least 25% are sexually active and so getting the vaccine at a reasonably early age is very-very important. Age 9 to 11 is the guideline that we would like to follow. Once one is exposed to the HPV virus, unfortunately the vaccine is not going to be effective. This is a prophylaxis vaccine, but if you have seen these young woman as I have who come in with these pre-malignant changes or warts, it is devastating emotionally to them. It is devastating to their families, it is something that simply has to be avoided if at all possible. I encourage everyone to consider the vaccine. I should also point out it has become available for boys as well.

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Chagpar We are going to come back to that conversation in a minute. We are going to take a break for a medical minute. Please stay tuned to learn more information about gynecologic cancers with myself and with Dr. Peter Schwartz.

Medical Minute

The American Cancer Society estimates that over the 1000 patients will be diagnosed with melanoma in Connecticut each year. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. Early detection is the key. When detected early, melanoma is easily treated and highly curable and new treatment options and surgical techniques are giving melanoma survivors more hope than they have ever had before. Clinical trials are currently underway at Yale Cancer Center, Connecticut's federally designated comprehensive cancer center, to test the innovative new treatments for melanoma. The specialized program of research excellence in skin cancer grant at Yale, also known as the SPORE grant, will establish national guidelines on modifying behavior and on prevention as well as identification of new drug targets. This has been a medial minute brought to you as a public service by Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by our guest Dr. Peter Schwartz. We are discussing gynecologic cancers. Dr. Schwartz, welcome back.

Schwartz Thank you very much.

Chagpar Before the break we were talking about HPV, which I understand is a virus that we now have a vaccine for that can prevent cervical cancer, but it has to be given before you develop cervical cancer. Are there other uses for the vaccine?

Schwartz Let me correct something, you have to receive it before you get exposed to the virus, not to the cancer. So, if someone is exposed to, the human papillomavirus then the vaccine will not be effective. So we try to give it to young women. But while cervix cancer is the disease that we most often focus on, it turns out the human papillomavirus is associated with a number of other sites for precancerous and cancerous changes. The second most common site that we would be involved with as gynecologic oncologist is the vulva, that is the tissue around the opening of the vagina and includes the labia majora, minora, and the clitoris, then the vagina, but we also see these HPV associated changes in the perianal area, and most recently it has been clearly described and associated with cancers of the oropharynx; that is the larynx in particular. HPV tends to get into sites where there is the common lining called the squamous epithelium, and HPV 16, one of

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about 100 different types of HPV, is the dominant one associated with genital cancers and cancers of the mouth and throat. We can prevent all of it presumably by taking the vaccine. So, it is worthwhile for both boys and girls.

Chagpar Terrific, and you had mentioned before the break as well that some of these cancers are associated with obesity. Are there other ways that we can try to prevent gynecologic cancers?

Schwartz Yes, absolutely. Obesity is the number one factor associated with uterine cancer, smoking, and sexual activities are associated with cancers of the cervix, vulva, and vagina. One has to really encourage a healthy lifestyle. It is believed that with a healthy lifestyle, meaning diet, exercise, avoidance of smoking, and excessive alcohol beverage intake, one could dramatically reduce the number of cancers one sees in the United States and for us, it is the cancers of the lower reproductive tract, the cervix, vulva, and vagina, that would be most affected by a reduction in smoking and alcohol ingestion and obesity is mainly associated with cancers of the uterus. If one was going to try to put together paradigms for reducing the likelihood of cancer in the reproductive tract, the use of birth control pills has been extremely effective in reducing ovarian cancer risk. If a woman is at increased risk for ovarian cancer, the use of birth control pills, which block ovulation, the release of the egg, appear to be intimately associated with reduction in the risk. We know that some women are at increased risk because of genetic mutations associated with the BRCA1 and BRCA2 gene and if one has those mutations, particularly starting in the teen years putting that young woman on birth control pills will help reduce her risk for ovarian cancer and of course it is true for the rest of the population as well. Birth control pills have also been associated with reduced risk of uterine cancer. But as I mentioned earlier, uterine cancer is not a major health hazard because of this obvious early warning symptom. Ovarian cancer has no obvious early warning symptoms. It is frequently mistaken for irritable bowel syndrome. There are only about 24,000 new cases of ovarian cancer a year but about 10% of Americans have irritable bowel. So when you come in to a doctor's office complaining of bloating, vague changes in your bowel habits, loss of appetite, or change in your appetite but no specific symptoms related to the ovary, most primary care doctors would say you have irritable bowel syndrome and it often results in a delay in the diagnosis. We are still looking for ways to detect ovarian cancer when it is involving only the ovary and quite honestly we have not been successful. There are ovarian cancer early detection programs and one of the very first in the country was started at Yale in 1990, and we still have to rely on pretty commonly available techniques like endovaginal ultrasound with color Doppler flow and CA 125 determinations. We have been working a numbers of years with Dr. Gil Mor in our research labs trying to identify new markers for the development of ovarian cancer. Initial results look great but when we tried it out clinically it did not appear to be quite as good as we thought and Dr. Mor continues to work with other institutions around the world to develop

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techniques to identify protein circulating in the blood stream that may be associated with an increased risk for ovarian cancer. For uterine cancer, the usual way of avoiding it is by not getting overweight and that is really very very important.

Chagpar And really really hard.

Schwartz Yeah. For cervical cancer, we have the screening technique of the Pap smear and there are some new techniques for Pap smears including the liquid cytology based techniques. It does not seem to matter much whether you use the older conventional type or the newer type of Pap smears. The important thing is to get screened. We had believed it very important that within six months of a woman becoming sexually active, she should start annual Pap smear screening. There are now new guidelines from the US Preventative Task Force and they now recommend not doing Pap smears before age 21, between age 21 and 30 Pap smears once every three years, and after age 30, one can combine the conventional Pap smear or liquid based Pap smear along with HPV determinations once every three to five years. I also recommend that women over age 65 who have had normal Pap smears in their reproductive ages and beyond do not need to have Pap smears beyond that age. Of course, all this is based on evidence based research but clinicians have to use their own clinical insight as well and for some individuals these guidelines are inappropriate and for myself if I have a young woman with markedly abnormal bleeding and pain that we can't quite understand, a Pap smear would be part of an evaluation that I might recommend. But basically the Pap smear screening does not need to be on an annual basis for women over aged 21, particularly those who are not at high risk for developing cervical cancer.

Chagpar It sounds like we have touched on some of the ways that we can prevent gynecologic cancers. We talked a little bit before the break about how we treat gynecologic cancers and one of the things that you had mentioned that I found very interesting was this aspect of surgery for fertility perseveration. I know that fertility perseveration is something that many women who are facing a variety of cancers have to deal with. Tell us a little bit more about some of the techniques that are available for fertility preservation.

Schwartz Let's start with ovarian cancer. There are different forms of ovarian cancer, but one of the rare forms that proved to be curative with chemotherapy, possibly the second cancer be cured with chemotherapy, is something we call germs cell tumors. When I was in my residency training program if a young woman came in with a yolk sac tumor, one of these rare tumors, her chance of living more than a year was about 10%. We now routinely cure all of these young women using common cytotoxic chemotherapy. That was a tremendous advance and what we showed at Yale is that not only could you cure these folks, you could preserve fertility. And we have published the

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largest series in the country of young women with stage III disease who are cured with removal of the cancer and usually just one ovary is involved so we can leave the other behind and we have given chemotherapy to these patients and they are not only cured, but they have children. There is a tumor called a dysgerminoma, which is the only ovarian tumor that is exclusively sensitive to radiation therapy. I was able to show that we can give chemotherapy to these patients and even when the other ovary was involved with the dysgerminoma I was able to preserve fertility and we have had a small series of patients who have had children, and so with rare tumors we are curing and preserving fertility. A common cancer is called an epithelial ovarian cancer and if it presents at stage I disease in a reproductive age woman, and the woman undergoes thorough surgical staging, which means we look all over the abdominal cavity for cancer, we remove a number of sites and biopsy a number of sites throughout the abdomen and retroperitoneal lymph nodes. If the patient truly has an early stage low grade tumor we do not need to remove the other ovary or the uterus, we can preserve fertility in that group of patients as well. Endometrial cancer typically occurs in postmenopausal women but in the 10% of women who are in the reproductive age, there is a role for hormonal therapy to try to preserve fertility, particularly in the more common low grade endometrial adenocarcinomas. Progestin therapy can reverse endometrial cancer and can change the lining of the uterus back to a normal uterus and in some of these patients they were able to conceive and carry a normal pregnancy. The most interesting and most dramatic of the changes has been a reduction in the radicality of cervical cancer in the management of stage I disease. I mentioned early about changing from a radical hysterectomy to a radical trachelectomy. Think of the uterus like a pear or a light bulb. The globular part is the body of the uterus and that is where the common cancer of the uterus is formed, but the narrow neck is the cervix, and one can remove about two thirds of the cervix and still preserve fertility and treat an invasive cervical cancer that is early in its a stage so that is really dramatic for us and we are very very happy about that.

Chagpar Tell me a little bit more also about the improvements that have happened both in terms of surgical techniques as well as chemotherapy and radiation. For a lot of different surgical procedures we have gone from making really big cuts to using holes, is that the kind of surgery that you do in gynecology as well?

Schwartz Yes, particularly for uterine cancer which is the dominant cancer that we see at Yale and it is most common in the pelvic reproductive organ cancers, the introduction of laparoscopy in my opinion robotic surgery has made a dramatic improvement. Our patients typically are very overweight, the heaviest patient I have had weighed about 520 pounds and we used the robot and that lady was ready to go home the next morning.

Dr. Peter Schwartz is John Slade Ely Professor of Obstetrics, Gynecology and Reproductive Sciences and Vice Chair of Gynecology at Yale School of Medicine. If you have questions or would like to add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.