Yale CANCER CENTER answers

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Cervical Cancer Screening Updates

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Yale Cancer Center Answers is a weekly broadcast on **WNPR** Connecticut Public Radio Sunday Evenings at 6:00PM

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Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert on Myelodysplastic Syndromes. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join in, you can e-mail your questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week it is a conversation about cervical cancer screening with Dr. Masoud Azodi. Dr. Azodi is Associate Professor of Obstetrics, Gynecology and Reproductive Sciences at Yale School of Medicine and here is Dr. Anees Chagpar.

Chagpar How about we start by talking about cervical cancer in general, how common it is and should women really be worried about this disease?

Azodi Yes, definitely, they need to be worried about it because it can be a significant disease but cervical cancer has had a great reduction in the number. In the last about 30 years, the number of cervical cancer has dropped by at least 50% in the United States and all the credit goes really to screening. We have excellent screening in this country and if we look at uterine cancer, we have about 35,000 cases a year, ovarian cancer about 25,000 but cervical cancer there are only about 13,000, still a significant number and that drop is really due to the screening program that we have here. When we look at other countries, worldwide, there are still about half a million cases of cervical cancer and it really gives credit to the screening programs.

Chagpar Tell us a little bit about screening because in a lot of malignancies, breast, colon, prostate, a lot of the guidelines have changed, so what is the deal with cervical cancer screening now? How often should women be screened and with what?

Azodi The cervix is a nice organ to be screened because it is an external organ in the vagina that can be screened and the Pap smear has been the mainstay of this screening. You are right, it has absolutely changed a lot because the number of Pap smears has dropped significantly because doing a Pap smear, a lot of times, we get abnormal Pap smears and it creates a lot of stress and worrying and we probably get over treatment because of the abnormal Pap smear. To decrease the over treatment, and also when you look at cervical cancer you need HPV, the human papilloma virus infection to develop cervical cancer in 99.9% of our cervical cancers, so therefore, screening with Pap smear and also HPV screening has become a big thing now. We have decreased the interval, so rather than doing it every year, now we do that at age 21, every 3 years as long as the Pap smear is normal. In the old days, we used to start the Pap smear at age 18 or whenever the woman became sexually active and that has completely changed. It does not matter about the sexual activity, we start at age 21, unless there are other risk factors. In an average risk woman, the Pap smear starts at age 21 regardless of their sexual activity and it is done every

3 years and after age 30, they can actually add the HPV screening. If they are HPV negative and the Pap smear is negative, they can do it at every 5-year screening and the screening with this stops at age 70, then does not continue unless there are other reasons, but actually there are new things where we use the HPV screening alone and it can be started at age 26; that is the new comer, that has not been the standard but that is something that in the future may be changed. We would not be talking about Pap smear, we would be talking about the HPV screening.

Chagpar And the HPV screen, is that a blood test?

Azodi No it is a Pap smear test, and we do what they call liquid cytology which can be used for screening the infection and also screening HPV which is considered to be basically a viral infection, but it is still a smear of the cervix at once and they use it either as just HPV alone or they can use it as Pap smear along with HPV testing at the same time.

Chagpar And with the whole concept of HPV, I suppose the other thing in terms of cervical cancer that may have contributed to the reduction in risk is now the vaccine for HPV. Do you think that has had an impact on incidence or is it too early still?

Azodi It is very early but you are right, our expectations are that it will have a significant effect. In Australia, everybody gets vaccinated, and they seem to have seen a reduction, but it is very early to say and actually here at least it is not standard to vaccinate boys, it is only for girls; my opinion is boys and girls both should be vaccinated, but you are right, over time when the vaccination becomes more and more common, then we would eventually see the reduction. My expectation is that over the next 20 years we should see a significant reduction.

Chagpar And so if HPV accounts for 99.9% of cervical cancers, if we vaccinate, if there was a program of universal vaccination, would that essentially mean that we wipe out cervical cancer altogether?

Azodi No, unfortunately not because we cannot vaccinate against all of the high-risk viruses. With HPV there are two categories, low-risk virus and high-risk virus. Low risk is not very significant and they do not do much. Most of the time when the ladies or even men get infected by the virus, most of the time they get immune to it and it is temporary and it goes away. When they become a persistent virus, that is when we worry about precancerous changes or dysplasia, but the high risk category, there are significant numbers of them and we have 3 vaccinations; one of them is what they call Bivalent which only vaccinates against HPV 16 and 18, which about 60% of our cervical cancers are caused by HPV 16 and 18. They probably would not eliminate but decrease significantly the number of cervical cancer that is caused by HPV 16 and 18, but the new vaccine we have, Quadrivalent, that comes 16 and 18 and also low risk for the warts

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and stuff but the new vaccine is a 9 virus. They have 7 high-risk viruses and 2 low risk which causes the vulvar condyloma and warts which should prevent that hopefully but yes, the expectation is about 70-80% of the cervical cancer that is caused by a high-risk virus would be vaccinated but still we would have about 20% of a cancer with other high-risk viruses that we are not vaccinating but there are some expectations and some studies that believe that they could have cross reactivity. Maybe you are right, eventually, it would decrease all of the high-risk viruses but there would be other high-risk viruses that we are not giving a vaccine against, at least we do not have it.

Chagpar So in that circumstance, if people have been vaccinated against HPV, should they still be screened with an HPV test because hopefully they never get HPV because they have now been vaccinated at least against the high-risk viruses or is Pap smear still going to be important to look for dysplastic changes?

Azodi At this point, the screening should stay as the standard regardless of the vaccination status because vaccination, the best age that I at least recommend is between ages 9 to 26, but the best time to give it is between 11 to 13, that is the best time for children because they have not had any sexual contact and it is also the best time for immune maturity at least that is what is believed, but I have to tell you, a lot of people probably have already had exposure before the vaccination and you are right, if everybody gets vaccination at a very young age universally, do we still need the screening? I think that remains to be seen, but currently, regardless of the vaccination, you still need the screening program and standard is Pap smear every 3 years or Pap smear and HPV testing after age 30 and every 5 years but the HPV screening alone has not become standard but it may become in future.

Chagpar And the HPV screening, does that include all of the viruses or just 16 and 18? If you have been vaccinated and the HPV testing only looks for 16 and 18, then it is not going to find it, correct?

Azodi You are absolutely right. At this point, they can just screen against all the HPVs which is not useful. They screen for high-risk HPV. And you can subcategorize, if somebody gets HPV screening alone and it is positive for high risk and if it is persistent, we know they are at high risk of cervical dysplasia. Those people you could do a colposcopy or Pap smear or you could break down and do a sub-specific, subtype and find if they are HPV 16 or 18 because we know that HPV 16 or 18 has a higher risk of cancer, we would watch them more closely and the screening does not mean they stay all with HPV screening; it should decrease the screening. Once they have persistent HPV, they still would need Pap smear, and still need a colposcopy to actually see and make sure they do not have lesions. Having HPV does not mean somebody will develop lesions. They are at risk for lesions. When you look at general HPV, about 80 to 90% of them, they become immune to it, about 10% are persistent and from them only a few get dysplasia and we understand that if we have a high-risk HPV persistent, then some of them,

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a significant number of them, will get dysplasia, but not everybody. Then those are a small category of the population, just decreases the screening number to a smaller number and those people may need a Pap smear or colposcopy at that time.

Chagpar So the HPV screening test is really to see whether you have got HPV and whether it is persistent and if it is persistent, then you need to have more aggressive Pap smear.

Azodi More aggressive screening or whatever needs to be done, yes.

Chagpar How does screening actually reduce the incidence then because, for example, in breast cancer when we screen people, we find that the incidence goes up because we are actually finding more cancers whereas in cervical cancer it is not quite that way, you are finding cancers before they become cancers.

Azodi This is actually ideal, to treat as a pre-cancer because pre-cancer of the cervix is very easily treatable and with Pap smear, or whatever method they use, you find it and you hopefully are finding them in a very early stage before they become actually cancer. We call it pre-cancer because they still are above the basement membrane or protective layer in our cells and they do not have the ability to metastasize and they can be treated locally by either ablation or cutting and that is still a procedure, but a very minimal procedure and you can actually treat the symptoms of the virus which is precancerous and the virus itself is taken care of by the vaccination or the women's own immune system, but what we are treating is the symptoms of a virus which is precancerous and if we treat the pre-cancer we would prevent actual cancer from developing and that is really the goal of screening. It is not to screen people, it is screen to prevent cancer and it has been very effective because the number of cervical cancers has dropped significantly and most of the people in the United States that get cancer, at least 50% of them have never had Pap smear before or screening and about 10% did not have screening in the last 5 years, that means only about 40% of our cancers are people that are getting screening, most of them might not be adequate screening and that is why screening is very effective because you do find them in a precancerous state and you do treat them locally and you do treat a lot of people in precancerous to prevent cancers.

Chagpar Tell us a little bit more about how precancerous lesions are treated with ablation or cutting, you mentioned. Is that a surgical procedure? Is that with general anesthetic or is this an office based procedure? What do women go through when they are having precancerous lesions treated?

Azodi Assuming a woman has an abnormal Pap smear, obviously depending on the severity, if it is a low grade or something nonsignificant, they would probably just follow her up with repeat Pap smear or repeat HPV testing. Assuming it is a significant lesion, they would undergo an office procedure called colposcopy. It is a little longer than the usual pelvic examination. They put a diluted vinegar solution in the cervix and they look under the magnifying glass and they look at the entire area on the cervix and

vagina to make sure there is no lesion. If there is no lesion, that would be great and they would just be observed, but if there is a lesion, they will undergo an office biopsy which is painful but not significant pain, it does not require any anesthesia and most ladies tolerate it very well with minimal pain and then we get the results of the biopsy. The results of the biopsy again categorizes this as a low-grade dysplasia or precancerous or high-grade. If they are low grade, we usually watch them, especially if they are younger that we do not want to do a lot of treatment on the cervix. In the higher graded lesion, they usually need a local treatment. Local treatment can be what they call ablative, you could just burn it with a laser or you could do what they call cryo freeze it which we do not use as much but is still being used and they both can be office procedures but usually laser these days are done in the operating room with a little bit of sedation or even mild general anesthesia. It is about a 5-10 minutes procedure. It is a very simple procedure, or they could do excision which is either cone biopsy or LEEP. LEEPs can be done in the office but sometimes we do that still under anesthesia, under sedation, but they are very quick procedures and local procedures.

Chagpar Excellent, thank you so much for giving us an overview of cervical cancer screening. We are going to talk a lot more about that after we take a short break for a medical minute. Please stay tuned to learn more information about cervical cancer with my guest Dr. Masoud Azodi.

Medical Minute *There are over 13 million cancer survivors in the United States and over 100,000 here in Connecticut. Completing treatment is an exciting milestone but cancer and its treatment can be a life-changing experience. Following treatment, cancer survivors can face several long term side effects of cancer 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 to help keep cancer survivors focused on healthy living. The Survivorship Clinic at Yale Cancer Center focuses on providing guidance and direction to empower survivors to maximize their health, quality of life and longevity. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to WNPR, Connecticut's Public Media Source for news and ideas.*

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined tonight by my guest Dr. Masoud Azodi. We are talking about cervical cancer and before the break, we talked a little bit about cervical cancer screening which is so important and has really resulted in a reduction in cervical cancer rates in this country and then we started talking about pre-cancers which is really why cervical cancer rates have declined, because they are so easily treatable when found with screening programs. Dr. Azodi, maybe we can pick up there and start talking a little bit about what happens when the screening finds more than a pre-cancer. Does it ever show an invasive cancer and what happens then?

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Azodi Yes, we do not want to see invasive cancer but unfortunately we do see it and we have 13,000 new cases of cervical cancer in the United States and as I already mentioned, most of these people have not had a screening in the past but there are some where they do get screening and they get cancer. We would like to find them in pre-cancers and treat as we mentioned but when they become invasive that is a different story and a different ball game. All of the pre-cancers are treated by a general gynecologist and once they become invasive cancer, they get referred to a gynecologic oncologist which is my specialty, and we treat cancer of women except breast cancer, and once they become invasive that means they have a potential to metastasize and leave the local area and potentially can cause severe morbidity for the patient and even mortality. The treatment is based on the stage of the disease. We would basically stage them, either they are very early, microscopic stage I, which is great and you can treat them with just a cone biopsy and if they still would like to carry a child and still want to keep their reproductive potential, they could still maintain it and be observed very close, but if they are let's say still not above the microscopic and they are 2 cm or less and they are still in reproductive age and they have a desire to have children, there is a procedure called radical trachelectomy. We actually do a radical surgery, remove the bottom part of the uterus which is the bottom neck of the uterus, we take that with some parametrial tissue which is the tissue around the cervix and we do a lymph node dissection. As long as we get a good margin and we get the lymph nodes negative, they can potentially preserve the uterus, still carry a child in the future, and that definitely would be a high-risk pregnancy on which there is a different topic that we can talk about, but they can still maintain the potential. That is very important to know for the reproductive age group and almost all of the obstetrician gynecologists in Connecticut are aware of that procedure. That would be for an early cancer where they still want to maintain their reproductive potential and want to carry a child in future.

Chagpar But can they have a vaginal delivery after that?

Azodi No, once you do that then you usually put what they call cerclage that maintains the baby within the uterus when they get pregnant, they do have a high risk of miscarriage, significantly higher than the general population, but they do still have a baby and carry a child but they will have C-section with their deliveries, absolutely. Now assuming they have invasive cancer and a visible lesion and they are not interested in future fertility or they are passed the fertility age, those people usually have what they call radical hysterectomy and that would be the uterus, cervix, and the parametrium comes with it and they still preserve the ovaries for their hormonal status and we do lymph node dissection and this can be done laparoscopically or with incision and now we usually like to do everything minimally invasively and in our specialty at Yale we really do most of the minimally invasive with laparoscope or robotic surgery and if we can get a good surgery and good margins, they can have a good survival and we still would follow it very closely, but they would not be able to carry a child because the uterus is gone, but if it is more advanced, unfortunately, we do see some more advanced cervical cancer in Connecticut, most of the

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people are migrants or people that have not had screening for a long time or some of them have ignored the symptoms because they have had abnormal bleeding and sometimes bleeding after sexual activity and intercourse, postcoital bleeding, and either they missed it or however, and they become advanced and surgery is not the option. They get treated with radiation and chemotherapy combination; as long as they are local disease, they can still be treated effectively and people still do well and have an acceptable quality life and with a decreased chance of recurrence. Unfortunately, if it becomes very advanced and becomes metastatic, meaning they travel outside the local area in the pelvis, then we need the systemic therapy with chemotherapy and prognosis becomes significantly worse because we really cannot treat them locally; we need to treat them systemically and in the early cancer as I said, surgery is the mainstay, but if somebody is not a good surgical candidate, chemotherapy and radiation can also substitute in early cancers also.

Chagpar That is interesting, so first of all who would not be a surgical candidate aside from comorbidities? Are there certain criteria of the tumor itself that make it unresectable such that you opt for chemotherapy and radiation?

Azodi Yes, depending first of all on the stage of the tumor which is clinically staged, the size of the tumor and also we get a chest x-ray usually to make sure there is no metastases to the chest and also an examination, is it traveling behind the cervix or is it within the cervix, what we call parametrium, that means the space between the cervix and the pelvis. If there is a tumor in it, that is really not a good surgical candidate. Once they become a stage that surgery by itself cannot cure it, then we just opt for chemotherapy and radiation.

Chagpar Even if you are resecting the parametrium?

Azodi Yes and if the tumor is a big size, then I cannot get a good margin or if the lymph nodes are positive, then I know that you are in need of radiation regardless, it is probably a better option, you just leave everything alone and treat with chemotherapy and radiation because we know that chemotherapy and radiation can be as effective as surgery. The reason for surgery is more rapid treatment and also eliminating the side effects of radiation.

Chagpar So let me get this straight. If you have got an early stage cervical cancer, all of our listeners who know where my head generally is, if you have got an early stage cervical cancer, I do not know too many women who love to go under the knife and if chemotherapy and radiation is equivalent to surgery, do you find women saying, no thank you to surgery or does surgery entail a better prognosis?

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Azodi No not definitely a better prognosis. Surgery is a better quality of life long term because radiation has more local effect on the bladder and rectum and risk of long-term effect on the sexual activity and bladder function and also risk of bowel obstruction in the future and yes, there are some that opt to do chemotherapy and radiation, but most younger people opt to do surgery.

Chagpar Which leads me to, let us suppose somebody presents and you think clinically they are fairly localized and you do surgery and at the time of your surgery that is when you are really taking out the lymph nodes and if the lymph nodes are involved, then what?

Azodi At least at Yale if the lymph nodes are involved, we stop the surgery. There are some places in the country where they still continue with radical surgery and what they believe is that it will give them better local control but at our practice and in most places, the practice is that if the lymph nodes are positive and you would know that the person would require radiation regardless, then we would stop it and we would not do the hysterectomy and we would stop the procedure and basically they will not delay their ultimate treatment which will be radiation and the morbidity of combination would be higher than just morbidity of radiation alone at that point.

Chagpar And so you check the lymph nodes during the operation with the frozen section.

Azodi Correct.

Chagpar So if the lymph nodes are involved does that mean that they need radiation or does that mean that they need chemotherapy as well?

Azodi Radiation for sure but there are studies that confirm that the combination of chemotherapy during radiation which is only about four weeks, once a week chemotherapy, low dose chemotherapy, has some systemic effect but we are looking at basically potentiating the radiation therapy effect. That is really not the significant side effect but makes the radiation more effective. Usually at this point, when the person needs radiation for cervical cancer, 90% of the time we do have chemotherapy given along with it for about 4-5 weeks.

Chagpar And so what about the people who have surgery alone, you do your surgery, you have got node negative, fairly small but invasive cancer, now a lot of our listeners know that invasive cancers as you say have passed the basement membrane, so they have access to blood vessels and lymph vessels. In those patients, do you ever give chemotherapy as well for the micro-metastatic spread that might ensue?

Azodi No, if the margins are positive which hopefully they are not; if the lymph nodes are positive or if let us say the parametrium, the tissue around that we took is positive, that means the tumor has left the cervical

area, those people would require radiation plus or minus chemotherapy but if the margins are negative, parametrium is negative, lymph nodes are negative and there is no other metastatic disease, then the radiation becomes only in few people if they have other high-risk factors, but that would be only probably about 20% of those people if they have a deep invasion to the cervix or if they have a large tumor, but about 70-80% of them would not require any other treatment and those people have excellent prognosis and they do very good long term.

Chagpar So they do not need chemotherapy?

Azodi Most of them would not need it if they have good margins and a small tumor, yes.

Chagpar So the only people who really need chemotherapy aside from potentiating the radiation are people with metastatic disease?

Azodi Metastatic disease with new systemic therapy or recurrent disease.

Chagpar Talk a little bit about what happens in the metastatic setting and in the recurrent setting. How is that treated?

Azodi That depends again on where it is coming back. If it is coming back locally, that means you have done the chemotherapy and not radiation, we usually wait about 3 months to make sure they get the full effect of radiation because radiation could still potentiate tumor death for a while. Let us say after six months or a year or so, I find my patient has a recurrent disease, at that point, it depends where the recurrence is. Let us say, recurrence is in the lung, that is a metastatic disease. At that point, systemic therapy is the option, which would be chemotherapy. We have all kinds of standard therapy, protocol therapy. There are few people that have isolated recurrences, it is very rare, we may still resect that but that is extremely rare, but as a general rule, if there is metastatic disease outside the local area, they will require systemic therapy but a lot of times, there would be just local recurrence. If there is local recurrence with no metastatic disease, they do have the option of surgical resection, and that would be what they call pelvic exenteration which is a big surgery. We remove the bladder, rectum and the vagina and uterus, everything, all in one unit and if it is a localized cyst, they can get cure out of that one, that is only for recurrence in the local disease.

Chagpar Wow, and so after people have had either radical trachelectomy or after they have had radiation and chemotherapy for a small potentially curative resection for a cervical cancer that is small, do they need to continue to have screening?

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Azodi Yes. Once you have cancer, for most of our gynecologic cancer, we do follow them and most of the time their recurrence usually is within the first two years after completion of therapy, ovarian cancer, uterine cancer, everything depending what the treatment is, chemotherapy or nothing, after the treatment could be just surgery alone as you said. We do watch them for the first two years very closely depending on the risk of recurrence, every two or three months for the first year, every three or four months for the second year. After two years, the risk of recurrence drops significantly, and then we change the appointments to every four to six months for five years and usually 95% of our recurrence happens within 5 years. If somebody does not recur after 5 years of completion of our treatment, the chance of recurrence is still there but significantly drops. Then at that point, the interval gets very prolonged, about a year or so.

Dr. Masoud Azodi is Associate Professor of Obstetrics, Gynecology and Reproductive Sciences at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written form at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.